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# Homogeneous coupling and carbonylation reactions of steroids possessing iodoalkene moieties. Catalytic and mechanistic aspects

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Dedicated to: The 70th birthday of Professor László Markó, in recognition of his contribution to cluster chemistry, coordination chemistry and homogeneous catalysis.

**Abstract**

Both 17-iodo-16-ene and 6-iodo-5-ene functionalities of androstane derivatives (17-iodo-4-aza-5α-androsta-16-en-3-one (**1**), 6-iodo-17-methoxycarbonyl-4-aza-androsta-5,16-dien-3-one (**2**), 6,17-diiodo-4-aza-androsta-5,16-dien-3-one (**3**), 17-iodo-androsta-16-ene (**4**), 6-iodo-17-(*N*,*N*-pentamethylene-carboxamido)-4-aza-androst-5,16-dien-3-one (**5**)) react with vinyl–tributyltin in a Stille reaction. However, palladium-catalysed carbonylation takes place selectively in position 17. The oxidative addition of 'iodo-vinyl' functionalities to in situ formed Pd(0)–triphenylphosphine species was observed by $^{31}$P-NMR spectroscopy. Dinuclear palladium(II) steroidal alkenyl or acyl species were detected under argon or carbon monoxide, respectively, when the 6-iodo-5-ene functionality (in ring B) was attached to a lactam moiety (ring A) in the steroidal substrate. In addition to monomeric species, some oligomeric ones were also formed depending on the reaction conditions (gas atmosphere, solvent). 

*Keywords:* Palladium; Phosphine; Steroids; Oxidative addition; Iodo-alkene

## 1. Introduction

Enol–triflates and vinyl halides (especially vinyl iodides) are among the most important synthetic building blocks used in various palladium-catalysed carbonylation and coupling reactions [1]. Although these reactions are widely used in synthetic organic chemistry, and the reaction mechanisms are the subject of a number of papers [2], some mechanistic details are still unclear.

The Pd(0)–monodentate phosphine systems proved to be some of the most active and versatile catalysts used in the above reactions and have been reviewed thoroughly [3–7]. The advantageous effect of bidentate phosphines on the reactivity of the catalyst is also well known. Heck [8] and asymmetric Heck reactions [9], nucleophilic substitution reactions [10–12] and carbonylative coupling [13] were performed by using the in situ catalyst formed from $Pd(OAc)_2$ and ditertiary phosphines.

The steroids with various functionalities are among the most valuable target compounds synthesised in homogeneous catalytic reactions for a long time [14]. Lately, 17-iodo-androsta-16-ene derivatives instead of the corresponding enol–triflates have been successfully used in our group for the synthesis of dienes [15], enines and carbonylated compounds [16], alkenylphosphonates [17], and dehalodimerization products [18]. There is much speculation as to the mechanism of these reactions, but the oxidative addition of the substrate onto coordinatively unsaturated palladium(0) species is generally accepted as a key step. The details of this

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process by using a simple androstane model compound and corresponding derivatives of pharmacological importance, as well as some aspects of the accompanying carbon monoxide insertion into palladium–alkenyl bond will be discussed.

## 2. Results and discussion

### 2.1. Catalytic vinylation and carbonylation reactions of steroidal iodoalkenes

The functionalised androstane derivatives (17-iodo-4-aza-5α-androsta-16-en-3-one (**1**), 6-iodo-17-methoxycarbonyl-4-aza-androsta-5,16-dien-3-one (**2**), 6,17-diiodo-4-aza-androsta-5,16-dien-3-one (**3**), 17-iodo-androsta-16-ene (**4**), and 6-iodo-17-(*N*,*N*-pentamethylene-carboxamido)

-4-aza-androst-5,16-dien-3-one (**5**), Fig. 1) possessing 'iodovinyl' functionalities in various positions, were used as substrates in Stille coupling with vinyltributyltin (Scheme 1).

Both 17-iodo-16-ene derivatives (**1**, **4**) and 6-iodo-5-ene compounds (**2**, **5**) react with moderate to high yields, resulting in the corresponding conjugated steroidal dienes (**1a**, **2a** and **4a**, **5a**, respectively) (Table 1).

Compound **3**, containing both 17-iodo-16-ene and 6-iodo-5-ene functionalities, underwent divinylation giving the 6,17-divinyl derivative (**3a**, Scheme 2) in 95% yield in 24 h using dimethylformamide as solvent. In toluene the reaction was slower: after 24 h beside the divinyl compound **3a** (13%), the 6-iodo-17-vinyl (**3a′**, 51%) and the 6-vinyl-17-iodo derivatives (**3a″**, 36%) were also detected (conversion: 88%) by GC-MS and NMR. The significant difference between reactivities of the mono (**1** **2**, **4**, **5**) and diiodo (**3**) compounds (see also Table 1) can be explained by the possible formation of 'tetranuclear species' as a result of oxidative addition of **3** onto the Pd(0) complex (see later).

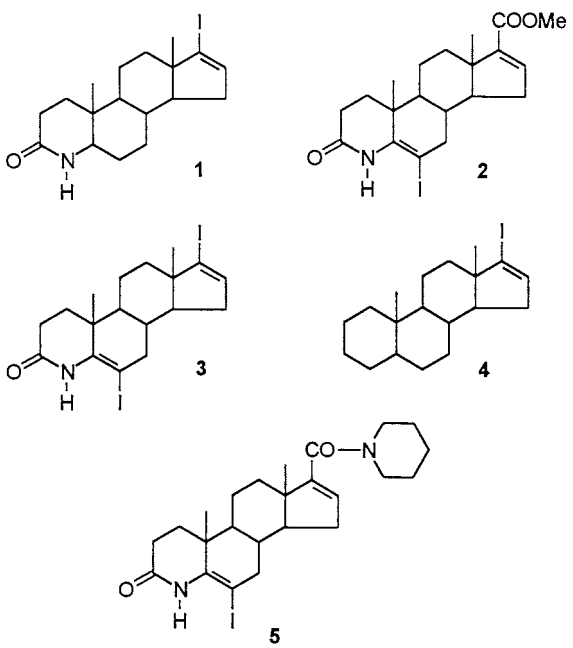
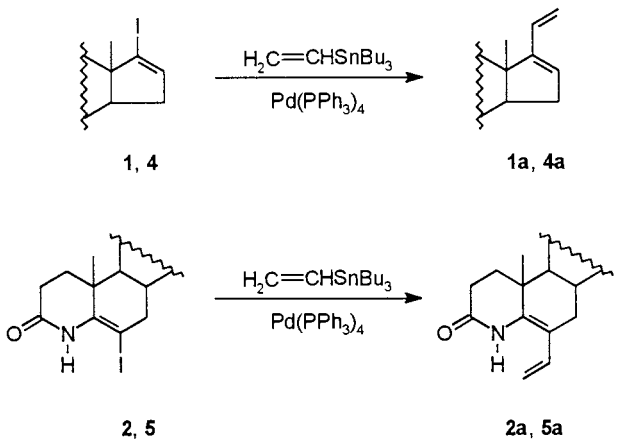



Fig. 1. Iodo-steroids used in homogeneous catalytic reactions and in the oxidative addition to palladium(0) species.



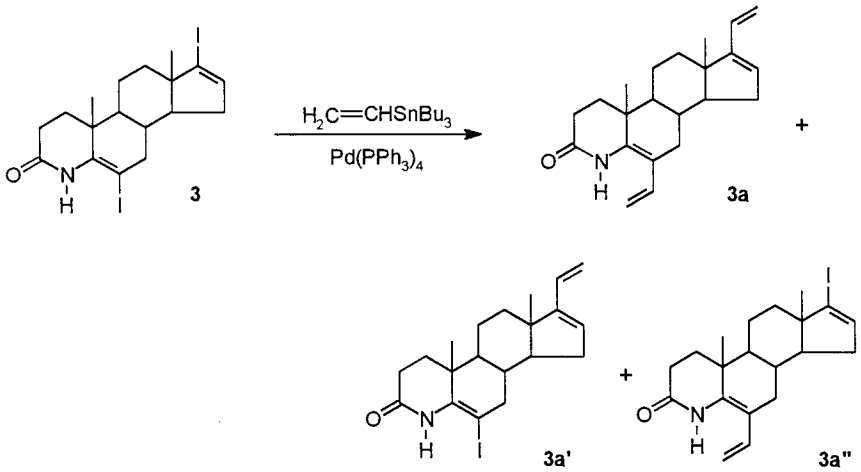

Scheme 1. Stille coupling by using 'iodo-vinyl' derivatives.

Substrate **3** was also used in aminocarbonylation and alkoxycarbonylation reactions (Scheme 3). In these cases, only the 17-iodo functionalities of the substrates were transformed to the corresponding 17-(*N*,*N*-pentamethylene–carboxamido) and 17-(methoxycarbonyl) derivatives leading to compounds **5** (95% yield) and **2** (98% yield), respectively. The 6-iodo substituent remained unchanged in the major product even after prolonged interaction. The 6-H derivative, formed through hydrodehalogenation, was obtained in traces. After the aimed aminocarbonylation of **2** and alkoxycarbonylation of **5**, most of the starting materials were recovered from the catalytic mixtures.

Table 1
Reaction of various steroidal iodo-vinyl derivatives with vinyltributyltin [a]

| Substrate | Reaction time (h) | Product | Yield (%) [b] |
|---|---|---|---|
| **1** | 24 | **1a** | 70 |
| **2** | 24 | **2a** | >98 |
| **3** | 24 | **3a** | 11 |
| **3** [c] | 24 | **3a** | 95 |
| **4** | 5 | **4a** | >98 |
| **5** | 24 | **5a** | 98 |

[a] Reaction conditions: catalyst, $Pd(PPh_3)_4$, Pd/substrate/vinyltributyltin = 0.02/1/1.1, 100°C, in toluene.
[b] Determined by GC.
[c] Solvent: DMF.




Scheme 2. Stille coupling by using **3** as a substrate.

The strikingly different behaviour of the 6- and 17-iodo substituents in oxidative addition onto palladium(0) in argon or carbon monoxide atmosphere was investigated by NMR spectroscopy.

### 2.2. Stoichiometric reactions of Pd(0) complexes with steroidal 'iodo-vinyl' derivatives under argon atmosphere

Although the low-ligated '$Pd(PPh_3)_n$' [3–6], formed in situ in the reaction of $Pd(OAc)_2$ and $PPh_3$, was found to be an efficient catalyst in the functionalisation of 'iodovinyl' substrates, little is known about the reaction mechanism.

The addition of **4** to '$Pd(PPh_3)$' resulted in the formation of Pd(II) species which proved to be easily detectable by $^{31}$P-NMR ($\delta = 13.4$ ppm). Due to the ligand exchange, a palladium–acetato complex instead of the corresponding iodo complex was also detected ($\delta = 13.0$ ppm, Eq. (2)).

$$\text{'Pd(PPh}_3\text{)'} + \text{–CH=C–I} \rightarrow \text{PdI(PPh}_3\text{)(C=CH–)} \quad (1)$$

$$\text{PdI(PPh}_3\text{)(C=CH–)} + \text{OAc}^- \rightarrow \text{Pd(OAc)(PPh}_3\text{)(C=CH—)} + \text{I}^- \quad (2)$$

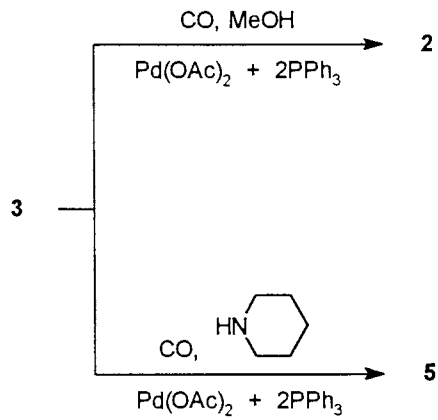
–CH=C–I = **1**, **4**

The $^1$H-NMR and GC-MS studies revealed that 5α-androsta-16-ene, the by-product of most of the catalytic reactions carried out with **4**, was present in the NMR solution after heating the solution at 60°C for 6 h. The origin of the hydrogen is still uncertain, although the acetic acid formed from the palladium precursor ($Pd(OAc)_2$) could serve as a proton source in NMR experiments and in part in catalytic reactions. A palladium–hydride species could split the palladium–carbon bond of the steroidal enyl–Pd species by the formation of dinuclear palladium complexes. The signals at 13–15 ppm in the $^{31}$P-NMR of the reaction mixture could be assigned to unstable dinuclear species [3].

In addition to the above low-ligated Pd(0) complexes, the $Pd_2(dba)_3 + 2\ PPh_3$ system was also used for the systematic investigation of the oxidative addition of various iodovinyl derivatives, such as 17-iodo-4-aza-5α-androsta-16-en-3-one (**1**), 6-iodo-17-methoxycarbonyl-4-aza-androsta-5,16-dien-3-one (**2**), and 6,17-diiodo-4-aza-androsta-5,16-dien-3-one (**3**) (Fig. 1).

Although $Pd(PPh_3)_4$ is a more active catalyst for Stille coupling than the in situ system formed from $Pd_2(dba)_3$ and $PPh_3$, probably because oxidative addition onto the former complex is much faster [5], the two precursors are supposed to give the same oxidative addition products. Spectra with $Pd(PPh_3)_4$ are usually rather complicated because of the exchange between the free and Pd(0)-coordinated phosphine. For these reasons the $Pd_2(dba)_3 + 2PPh_3$ system was chosen for the mechanistic investigations.

Oxidative addition of **1** took place to $Pd(dba)(PPh_3)_2$ ($\delta = 25.8$, 27.7 ppm) under argon, resulting in a sharp signal at 16.8 ppm (Fig. 2) [19]. The spectrum corresponds to a *trans*-bis(triphenylphosphino)-iodo-'enyl'-palladium(II) complex, $\mathbf{1a}_{17}$ (Fig. 3).




Scheme 3. Alkoxycarbonylation and aminocarbonylation reactions of **3**.

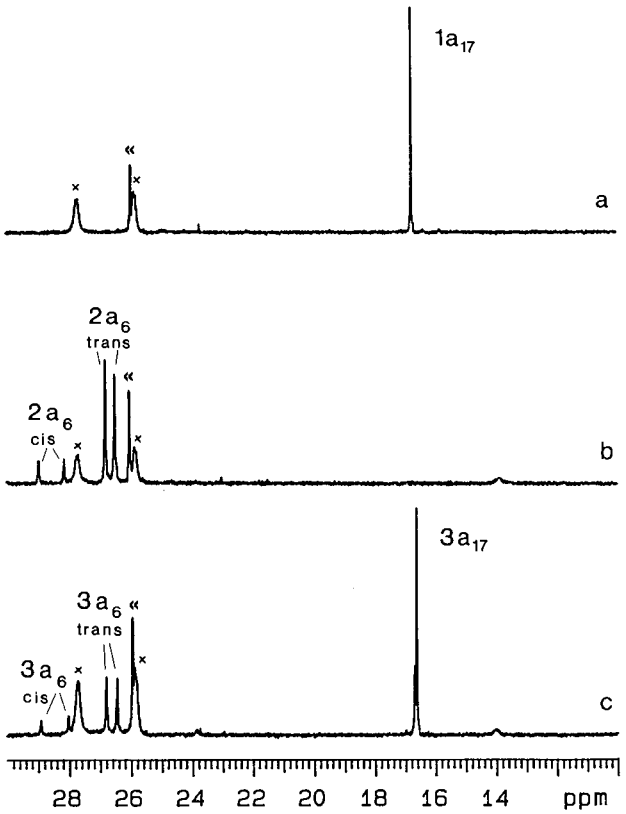



Fig. 2. The $^{31}$P-NMR of the reaction mixture of iodovinyl derivatives in DMF-$d_7$ under argon at room temperature using $Pd_2(dba)_3$ precursor. Keys for the figure: (a) $Pd/PPh_3/\mathbf{1} = 1/2/1$; (b) $Pd/PPh_3/\mathbf{2} = 1/2/1$; (c) $Pd/PPh_3/\mathbf{3} = 2/4/1$ (x and « stand for $Pd(dba)(PPh_3)_2$ and $P(O)Ph_3$, respectively. The subscripts indicate the position of the reacting iodo-substituent).

However, the oxidative addition of **2** (6-iodo-$\Delta^6$ derivative) and **3** (possessing both 17-iodo-16-ene and 6-iodo-5-ene functionalities) gave more complicated spectra. The reaction mixture of **2** consists of two pairs of singlets at $\delta_1 = 26.4$ ppm, $\delta_2 = 26.8$ ppm and $\delta_3 = 28$ ppm, $\delta_4 = 28.9$ ppm. The reaction of the 6-iodo-5-ene moiety with Pd(0) species yielded two species possessing

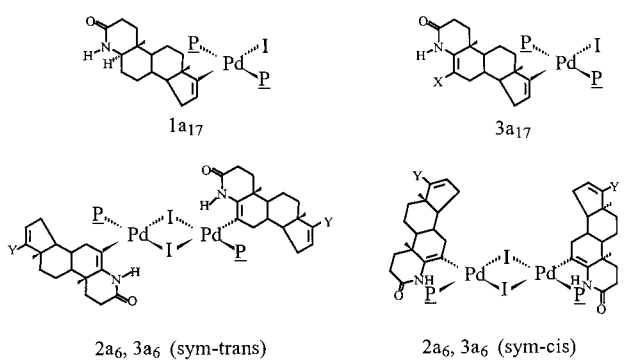



Fig. 3. The proposed structures of palladium–alkenyl complexes present in the in situ reaction mixtures of $Pd_2(dba)_3$ with iodovinyl steroids (**1**, **2**, **3**) under argon. (P stands for $PPh_3$; X = 'PdIP'; Y = COOMe in $\mathbf{2a}_6$ and Y = I or '$PdIP_2$' in $\mathbf{3a}_6$).

two chemically different phosphines ($\mathbf{2a}_6$). Since there is no coupling between the phosphorus, the formation of two dinuclear iodo bridged complexes was supposed [20]. The major component ($\delta_1$, $\delta_2$) has the two phosphine ligand in *sym–trans*, while the minor one ($\delta_3$, $\delta_4$) in *sym–cis* position (Figs. 2 and 3).

The pair of signals in the case of both isomers can be explained by the different disposition of the chiral steroidal backbone. The most probable explanation is as follows. The steroidal alkenyl ligand may be 'fixed' in two different positions by the lactam coordination: (i) the phosphine is on the β-side of the steroid (the 19-methyl pointing towards the phosphine sitting in the *cis* position); (ii) the phosphine is on the α-side of the steroid (19-methyl pointing away from the phosphine) (Fig. 3). In the case of $\mathbf{2a}_6$ (*sym–trans*, major isomer) one of the two lactam moieties is situated above the $(Pd–I)_2$ plane, the other is below the plane, resulting in two chemically nonequivalent phosphine due to their β- and α-side disposition, respectively. The minor component ($\mathbf{2a}_6$ (*sym–cis*)), which is formed in situ from $Pd_2(dba)_3$, triphenylphosphine and **2**, possesses steroidal alkenyl ligands, which probably have the lactam moieties (A ring) on the same side of the dinuclear core. It means that one phosphine is situated on the α-, while the other on the β-side of the steroidal skeleton.

The spectrum obtained with **3** can be considered as a surprisingly good superposition of the spectra obtained with **1** and **2** indicating the reaction of both iodovinyl functionalities. The signal detected at 16.8 ppm characterises a Pd(II) species as a result of the oxidative addition of 17-iodo-16-ene moiety ($\mathbf{3a}_{17}$). When the reaction was carried out by using $Pd/\mathbf{3} < 2$ ratio, the signal assigned to $\mathbf{3a}_{17}$ ($\delta = 16.8$ ppm) was the dominating one in the spectrum. This fact refers to the higher reactivity of 17-iodo-16-ene than that of the 6-iodo-5-ene moiety. While the reaction of $Pd_2(dba)_3$ and $PPh_3$ with **1** resulted in one singlet at 16.8 ppm, using **3** several (at least three) singlets appeared. These are assigned to a more complicated structure, where the 6-iodo-5-ene moiety of $\mathbf{3a}_{17}$ reacts further with Pd(0) species to form a 'tetranuclear species'. The four singlets in the downfield region ($\delta_1$, $\delta_2$, $\delta_3$, $\delta_4$) are due to the coincidence of signals of the phosphorus atoms in the $(Pd—I)_2$ plane of both $\mathbf{3a}_6$ (Y = I or '$PdP_2I$') complexes.

### *2.3. Stoichiometric reactions of Pd(0) complexes with steroidal 'iodo-vinyl' derivatives under carbon monoxide atmosphere*

The oxidative addition–carbon monoxide insertion reaction sequence was investigated by carrying out similar experiments under a carbon monoxide atmosphere. Although in carbonylation reactions the $Pd(OAc)_2 + n PPh_3$ 'in situ' catalyst was the most effective, for the

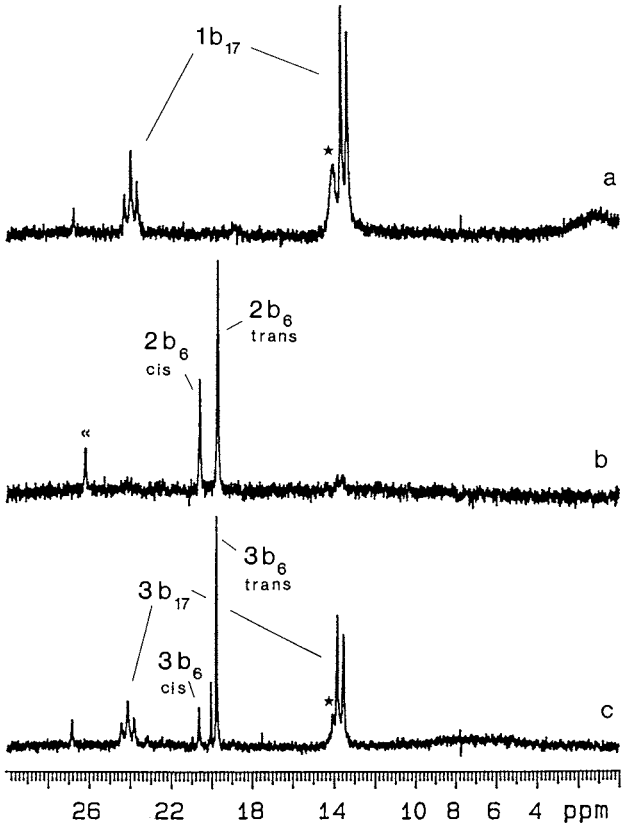



Fig. 4. The $^{31}$P-NMR of the reaction mixture of iodovinyl derivatives in DMF-$d_7$ under carbon monoxide at room temperature using $Pd_2(dba)_3$ precursor. Keys for the figure: (a) $Pd/PPh_3/\mathbf{1} = 1/2/1$; (b) $Pd/PPh_3/\mathbf{2} = 1/2/1$; (c) $Pd/PPh_3/\mathbf{3} = 2/4/1$ (* and « stand for *trans*-$PdI_2(PPh_3)_2$ and $P(O)Ph_3$, respectively).

NMR investigations the simpler $Pd_2(dba)_3 + nPPh_3$ system, which also proved to be an active catalyst, was used.

No palladium–alkenyl complexes were detected under carbon monoxide in the case of **1**–**3**. This refers to fast CO insertion into the palladium–steroidal enyl bond. The reaction with **1** yielded a mononuclear palladium species possessing three phosphorus, two of them equivalent (13.45 ppm (d, 2P); 23.9 ppm (t, 1P); $J_{P-P} =$ 36 Hz, Fig. 4). A broad singlet can be observed in the spectrum at 14 ppm which proved to be *trans*-$PdI_2(PPh_3)_2$ (X-ray crystallography; $^{31}$P-NMR (13.48 ppm, $CDCl_3$)) and a very broad signal near 1 ppm ('$Pd(PPh_3)_n$'). The doublet–triplet pair was assigned to an acyl complex, $\mathbf{1b}_{17}$ (Fig. 5), which possesses no iodine ligand. The unexpected structure was proposed on the basis of the following facts: (i) The $^1$H-NMR shows steroidal moiety bound to palladium. No sign of unreacted **1** was detected. The most informative steroidal signals: 19-$CH_3$ (0.92 ppm), 18-$CH_3$ (0.95 ppm) and 16-H (6.68 ppm) show the presence of only one such compound. The chemical shift of 16-H refers to the presence of a CO attached to C-17. (ii) Since approximately half of the palladium is present in *trans*-$PdI_2(PPh_3)_2$ and Pd(0) species, the acyl complex must contain more than one steroidal ligand. (iii) The ratio of $\mathbf{1}/PPh_3$ is 1/2 in the starting reaction mixture and some $PPh_3$ is involved in the above two 'steroid-free' complexes. As a consequence of that, the ratio of steroid to $PPh_3$ must be 2/3 and not 1/3 in $\mathbf{1b}_{17}$. (The latter ratio could result also in a complex characterised by a doublet–triplet pair in $^{31}$P-NMR.) The iodine–steroidal alkenyl exchange is supported by the presence of this complex in the reaction mixture and by iodine formation via reductive elimination. A similar phenomenon was observed during NMR investigation of $PtI_2P_2$ complexes (where $P_2$ stands for a bidentate or two monodentate phosphines) [21]. The addition of secondary amines to the NMR samples gives rise to the formation of the corresponding steroidal amides (GC-MS).

The $^{31}$P-NMR of the acyl complex obtained from **2** refers to the presence of two species at a ratio of ca. 1/2. Since both complexes possess a singlet only (19.8 and 20.6 ppm), two dinuclear acyl complexes with two phosphines in '*trans*' and in '*cis*' position ($\mathbf{2b}_6$ (*sym–trans*) and $\mathbf{2b}_6$ (*sym–cis*)) are proposed, respectively. Surprisingly, no indication for the 'duplication' of the lines attributed to the different disposition of the steroidal moieties was observed. It could be explained by the 'opposite side' coordination of the lactam functionalities in $\mathbf{2b}_6$ (*sym–cis*), and by the same side disposition of the lactam functionalities (and consequently the C–D rings) in $\mathbf{2b}_6$ (*sym–trans*) (Fig. 5).

The spectrum of the reaction mixture obtained by using **3** contains all the characteristic signals of the above two spectra. It is worth noting that the ratio of the two singlets is completely different from that obtained with **2**. Because of the coordination of position 17 to another palladium (the presence of 16-en-17-yl–palladium–phosphine moiety), the steroidal ligand be-

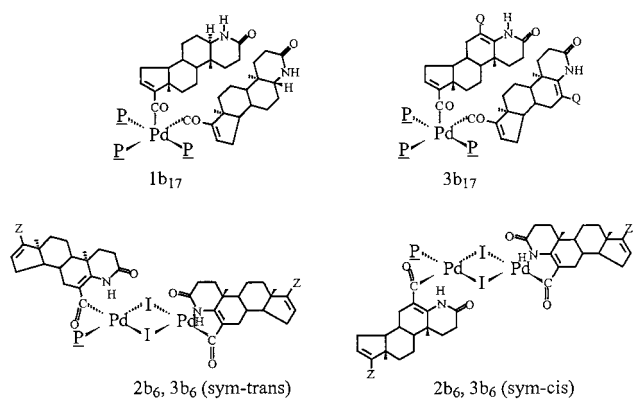



Fig. 5. The proposed structures of palladium–acyl complexes present in the in situ reaction mixtures of $Pd_2(dba)_3$ with iodovinyl steroids (**1**, **2**, **3**) under carbon monoxide. (One of the two phosphorus atoms is hidden by the A,B rings of the steroid; P stands for $PPh_3$; Q = 'PdIP'; Z = COOMe in $\mathbf{2b}_6$ and Z = I or '$PdP_3$' in $\mathbf{3b}_6$).

comes bulkier and the *sym–trans*/*sym–cis* ratio increases.

The further reaction of the 6-iodo-5-ene functionality of $\mathbf{3b}_{17}$ can be proved by high resolution $^{31}$P-NMR spectra, where the signal of the phosphorus atoms in the (Pd—I)$_2$ plane ($\delta = 19.8$ ppm) shows a splitting ($\Delta\delta = 0.018$ ppm). In contrast to the experiments carried out under argon, the signals of the 'plane-in' phosphorus atoms indicate the oxidative addition of both iodovinyl-functionalities (17-iodo-16-ene and 6-iodo-5-ene).

It is worth noting that further reaction of the acyl complexes with nucleophiles takes place only in position 17 of the steroidal substrate. For example, no 6-carboxamido androstanes could be detected in the reaction of $\mathbf{3b}_6$ or $\mathbf{2b}_6$ with primary and secondary amines.

In $\mathbf{3b}_6$, the steroidal moiety can serve as a chelating ligand through coordination of the lactam nitrogen. This coordination is supposed to be stronger here than in the case of $\mathbf{3a}_6$ because of the favourable ring size. This leads to a complex with a rather crowded metal centre that is less capable to react with a nucleophile. Supposing a facile decarbonylation–reductive elimination sequence for $\mathbf{3b}_6$ giving rise to the formation of a palladium(0) species and an iodo-vinyl steroid, the metal centre is able to undergo a new oxidative addition of the 17-iodo functionality of another steroid molecule and to afford a carbonylation product.

## 3. Experimental

$^{31}$P-NMR spectra were recorded on a Varian Unity spectrometer (121.4 MHz). All of the experiments were carried out under argon. GC-MS measurements on steroids were performed with a Hewlett–Packard 5971A GC-MSD using a HP-1 column.

### 3.1. Chemicals

The NMR solvents (toluene-$d_8$, DMF-$d_7$) were purchased from Fluka and were used after standard purification under argon. Pd(OAc)$_2$ and PPh$_3$ were from commercial sources (Aldrich and Fluka, respectively) and were used without further purification. Pd$_2$(dba)$_3$·CHCl$_3$ was prepared as described in the literature [22].

The steroidal iodovinyl derivatives were prepared from the corresponding ketone via the hydrazon [23].

### 3.2. Catalytic experiments

#### 3.2.1. Stille coupling of steroidal alkenyl iodides

Pd(PPh$_3$)$_4$ (0.02 mmol) and the steroid (1 mmol) were added to a flask equipped with a reflux condenser and a septum inlet. The flask was flushed with argon and charged with 10 ml of toluene (or DMF). A total of 1.1 mmol of vinyltributyltin was added by means of a hypodermic syringe through the septum inlet. The mixture was stirred at 100°C. The reaction was followed by GC and TLC. After completion of the vinylation, an aqueous solution of 1.5 mmol KF was added and the mixture was stirred overnight. The organic layer was separated and dried over $Na_2SO_4$. The product was purified after removal of the solvent by chromatography on silica gel (eluent: 9:1 chloroform–methanol). The structures of the isolated compounds were determined by $^1$H-NMR spectroscopy, elemental analysis, and MS.

#### 3.2.2. Carbonylation reactions of steroidal alkenyl iodides

In a typical procedure, a mixture of the steroid (1 mmol), piperidine (or methanol) (5 mmol), Pd(OAc)$_2$ (0.05 mmol), PPh$_3$ (0.1 mmol) and Et$_3$N (3 mmol) were allowed to react in DMF under carbon monoxide at 60°C. The reaction was monitored by GC and TLC. When the reaction was completed, the solvent was removed in vacuum. The residue was dissolved in 20 ml of CHCl$_3$, washed with two portions of 20 ml 5% HCl, 20 ml of saturated aqueous NaHCO$_3$, and brine and dried over $Na_2SO_4$. The product was purified by chromatography on silica gel (eluent: 9:1 chloroform–methanol). The structures of the isolated compounds were determined by $^1$H-NMR spectroscopy, elemental analysis, and MS.

### 3.3. Preparation of the samples for NMR investigations

In a typical experiment, the preparation of the NMR sample was carried out as follows: 0.02 mmol steroid, 10.3 mg (0.01 mmol) Pd$_2$(dba)$_3$, and 10.5 mg (0.04 mmol PPh$_3$), were placed into a three-necked flask equipped with a magnetic stirrer, a septum inlet, a gas inlet, and a reflux condenser with a balloon on the top. It was placed under argon or carbon monoxide and 0.7 ml DMF-$d_7$ was added. The reaction was conducted under argon for 1 h at 60°C (or under carbon monoxide for 0.25 h at 60°C). The pale brown or dark red solution (under argon or carbon monoxide, respectively) was transferred by a cannula into the NMR tube under the same atmosphere as the reaction had been performed.

### 3.4. Analytical data of the products

#### 3.4.1. 6-Iodo-17-methoxycarbonyl-4-aza-androsta-5,16-dien-3-one (**2**)

$^1$H-NMR (CDCl$_3$): $\delta$ 7.42 (brs, 1H, NH), 6.77 (m, 1H, 16-H), 3.73 (s, 3H, OCH$_3$), 2.74 (m, 1H, 7-H$_a$), 2.50

(m, 2H, 2-$H_2$), 1.2–2.4 (m, 12H, ring protons), 1.15 (s, 3H, 19-$H_3$), 0.95 (s, 3H, 18-$H_3$); MS (*m*/*z*, rel.int.): 455/80 [$M^+$], 440/12 [$M^+ - CH_3$], 149/27, 100/89, 72/100, 57/51. Anal. Calc. for $C_{20}H_{26}NO_3I$ (455.34): C, 52.76; H, 5.76; N, 3.08. Found: C, 52.55, H, 6.05; N, 3.34. Yield: 68%.

*3.4.2. 6-Ethenyl-17-methoxycarbonyl-4-aza-androsta-5,16-dien-3-one (**2a**)*

$^1$H-NMR ($CDCl_3$): $\delta$ 7.45 (brs, 1H, NH), 6.78 (m, 1H, 16-H), 6.55 (dd, 11 Hz, 17 Hz, 1H, 6′-H), 5.16 (d, 17 Hz, 1H, 6″-$H_b$), 5.09 (d, 11 Hz, 1H, 6″-$H_a$), 3.70 (s, 3H, $OCH_3$), 2.52 (m, 2H, 2-$H_2$), 1.15–2.4 (m, 13H, ring protons), 1.08 (s, 3H, 19-$H_3$), 0.95 (s, 3H, 18-$H_3$); FAB MS: 356 [$M^+ + H$]. Anal. Calc. for $C_{22}H_{29}NO_3$ (355.48): C, 74.33; H, 8.22; N, 3.94. Found: C, 74.15, H, 8.51; N, 4.19. Yield: 57%.

*3.4.3. 6-Ethenyl-4-aza-pregna-5,16,20-trien-3-one (**3a**)*

$^1$H-NMR ($CDCl_3$): $\delta$ 7.35 (brs, 1H, NH), 6.54 (dd, 11 Hz, 18 Hz, 1H, 6′-H), 6.32 (dd, 12 Hz, 18 Hz, 1H, 20-H), 5.75 (m, 1H, 16-H), 5.33 (d, 18 Hz, 1H, 21-$H_b$), 5.19 (d, 18 Hz, 1H, 6″-$H_b$), 5.12 (d, 11 Hz, 1H, 6″-$H_a$), 4.99 (d, 12 Hz, 1H, 21-$H_a$), 2.50 (m, 2H, 2-$H_2$), 1.2–2.4 (m, 13H, ring protons), 1.10 (s, 3H, 19-$H_3$), 0.92 (s, 3H, 18-$H_3$); MS (*m*/*z*, rel.int.): 323/100 [$M^+$], 308/26 [$M^+ - CH_3$], 267/27, 117/44, 91/56, 67/44, 55/84. Anal. Calc. for $C_{22}H_{29}NO$ (323.48): C, 81.69; H, 9.04; N, 4.33. Found: C, 81.40, H, 9.32; N, 4.58. Yield: 64%.

*3.4.4. 6-Iodo-17-(N,N-pentamethylene-carboxamido)-4-aza-androst-5,16-dien-3-one (**5**)*

$^1$H-NMR ($CDCl_3$): $\delta$ 7.38 (brs, 1H, NH), 5.73 (m, 1H, 16-H), 3.52 (m, 4H, N($CH_2$)), 2.73 (dd, 6 Hz, 18 Hz, 1H, 7-$H_a$), 2.50 (m, 2H, 2-$H_2$), 2.35 (dd, 13 Hz, 18 Hz, 1H, 7-$H_b$), 2.26 (m, 1H, 15-$H_a$), 1.3–2.4 (m, 16H, ring protons), 1.15 (s, 3H, 19-$H_3$), 1.08 (s, 3H, 18-$H_3$); MS (*m*/*z*, rel.int.): 508/5 [$M^+$], 493/3 [$M^+ - CH_3$], 183/25, 149/20, 112/70, 84/100, 69/85, 41/70. Anal. Calc. for $C_{24}H_{33}N_2O_2I$ (508.44): C, 56.70; H, 6.54; N, 5.51. Found: C, 56.41, H, 6.78; N, 5.82. Yield: 78%.

*3.5. 6-Ethenyl-17-(N,N-pentamethylene-carboxamido)-4-aza-androst-5,16-dien-3-one (**5a**)*

$^1$H-NMR ($CDCl_3$): $\delta$ 7.42 (brs, 1H, NH), 6.54 (dd, 11 Hz, 17 Hz, 1H, 6′-H), 5.75 (m, 1H, 16-H), 5.19 (d, 17 Hz, 1H, 6″-$H_b$), 5.12 (d, 11 Hz, 1H, 6″-$H_a$), 3.58 (m, 4H, N($CH_2$)), 2.52 (m, 2H, 2-$H_2$), 1.2–2.4 (m, 19H, ring protons), 1.15 (s, 3H, 19-$H_3$), 1.10 (s, 3H, 18-$H_3$); MS (*m*/*z*, rel.int.): 408/100 [$M^+$], 393/32 [$M^+ - CH_3$], 382/25, 367/20, 55/45. Anal. Calc. for $C_{26}H_{36}N_2O_2$ (408.58): C, 76.43; H, 8.88; N, 6.86. Found: C, 76.22, H, 9.12; N, 7.17. Yield: 48%.

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