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Cyclopalladation of phenols in the form of mixed phosphite esters

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Abstract

Phenols can be cyclopalladated after being converted into dialkoxy-O-phosphite esters. The usefulness of this novel synthetic method has been demonstrated on the examples of natural phenols, L-(+)-tyrosine and (+)-estrone. The molecular structure of cyclopalladated estrone has been determined using an X-ray method. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Cyclopalladation; Estrone; Phenols; Phosphites; Tyrosine; X-ray molecular structure

1. Introduction

Molecular design requires synthetic methods for the directed structural modification of certain parent molecules. This is important in examples of bioactive molecules when the 'structure–activity' correlation is studied. Functional groups already present in the molecule are often used for introducing other groups into specific positions.

Among the most useful reactions is cyclometalation because it allows activation of particular positions using a cyclic array of a limited numbers of atoms (usually five or six). The metal introduced can be then exchanged for a variety of different groups σ-bonded through carbon or a heteroatom. In particular, cyclopalladation has found the broadest application in organic synthesis due to the readiness of the procedure and the high reactivity of the carbon–palladium bond. Many reviews of this reaction are available (see Ref. [1] for example).

A general scheme of cyclometalation with the substitution of a hydrogen atom for a metal had been formulated by us early in 1973 [2]. It includes specific tetrades of atoms C–X–Y–Z wherein C is bonded to a hydrogen to be replaced, while Z is a directing atom with a lone electron pair coordinated to the metal (Fig. 1(a)). The most important case is when both C and X=C are incorporated into an aryl system (Fig. 1(b)), as was the case in the very first examples found [3,4]. Cyclopentadienyl ligands in π-metal complexes can undergo the same reaction [5,6].

Cyclometalation is not possible if there is no directing atom Z in a suitable position. For M = Pd or Pt, Z is usually N or P, rarely S. Until present, one of the widespread functions, phenolic hydroxyl, could not be used as a directing group in cyclometalation. Until very recently, the only metal-assisted regioselective *ortho*-substitution known in phenols was a classical Kolbe synthesis of salicylic acid from sodium phenolate [7], which cannot be considered as a typical cyclometalation.

1.1. Phenolic hydroxyl can be converted into a directing group for cyclopalladation

In order to make the phenol function suitable for cyclometalation, it must be modified by replacing hydrogen in the OH group for an atom which could coordinate the metal and promote its attack into the *ortho*-position of the aryl ring. Phosphorus(III) seems to be a good candidate for this purpose.

In this paper we wish to report the use of phenolic hydroxyl in the form of a mixed dialkoxy(aryloxy)phosphite as a directing group for cyclopalladation into a neighboring (*ortho*) position of the same

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aryl ring (see Ref. [8] for a preliminary communication). This approach is based on the report of Albinati et al. [9] on the cyclopalladation of triphenylphosphite in which only one aryl group underwent *ortho*-substitution. However, for an effective application as a synthetic method, phenol should be converted into a mixed phosphite ester with two inert alkoxy groups. We have chosen two naturally occurring phenols, L-(+)-tyrosine and (+)-estrone, to demonstrate the usefulness of this approach (Fig. 2).

Tyrosine is of particular interest because its derivatives, having other substituents in the phenyl ring neighboring the hydroxyl group, are of high biological and medical significance, such as 3,4-dihydroxy-L-phenylalanine (L-DOPA) or thyroxine, a derivative of 3,5-diiodo-L-tyrosine. In addition, there is a family of antibiotics whose structure is based on so-called 'di-tyrosine', in which the second O-tyrosine moiety is linked to 3-aryl position of the first one [10]. A convenient method for introducing the metal in to an *ortho*-position relative to the hydroxyl may open the way to 3-heteroatomic derivatives of tyrosine. Both the 3- and 5-positions in tyrosine are equivalent.

Estrone is a representative of the steroid hormones family. Aryl part of the estrone molecule (ring A) is structurally non-symmetrical, the two *ortho*-positions being different and two isomers of cyclometalated compound are possible. Introduction of any substituents adjacent to the hydroxyl group can influence the biological activity of estrone in an unknown way.

2. Results and discussion

Treatment of *N*-acetyl-L-tyrosine ethyl ester with $(AlkO)_2PCl$ or with pyrocatechol chlorophosphite did not give the desired tyrosine phosphites as isolable products. A successful procedure was achieved when a phenol was heated with dialkyl *N*,*N*-diethylphosphoramidite, $(EtO)_2PNEt_2$, without any solvent.

O-Diethoxyphosphito-[*N*-acetyl-L-tyrosine ethyl ester] (**1**) was obtained as a pure compound in quantitative yield and was fully characterized. It is worth noting that Perish and Jones had previously performed a similar reaction in solution but it was catalyzed by tetrazols [11,12]. However, they did not isolate the O-phosphites of protected L-tyrosine but oxidized them in situ to the corresponding O-phospho-L-tyrosine derivatives for the purpose of peptide synthesis.

Using **1** as a P-ligand, complexes of the type L_2PdCl_2 (**2**) have been readily prepared, which can then be converted into the cyclopalladated derivative **3** on boiling with an excess of $PdCl_2$ in toluene according to the procedure described in Ref. [9] (Fig. 2).

The same reaction sequence has been applied for (+)-estrone. O-Diethoxyphosphino-(+)-estrone (**4**) has been converted to the L_2PdCl_2 complex (**5**), from which two regioisomers of the cyclopalladated compounds (**6**) have been formed (in a 1:3 ratio), which differ in solubility and in $^{31}P\{^1H\}$-NMR chemical shifts, i.e. δ 130.7 ppm for **6a** and δ 131.8 ppm for **6b** (Fig. 2). It was possible to isolate the major isomer, **6b**, by fractional crystallization as verified by NMR and X-ray analysis of a single crystal was performed.

X-ray investigation has shown (Fig. 3, Tables 1–3) that **6b** is a cyclopalladated dimer with two steroidal polycyclic fragments (A and B). Two Pd(II) atoms in **6b** are involved in a square planar coordination with two bridged chlorine atoms and with the phosphorus and carbon atoms. Deviations of the Pd(1) and Pd(1′) atoms from the plane of four substituents are −0.02 and 0.006 Å, respectively. Bond lengths of the Pd atoms have typical values (see Table 2 and Ref. [13]). The puckering angle of Pd(1)–Cl(1)–Cl(1′)–Pd(1′) ring is 30°.

The heterocyclic five-membered Pd(1)–C(2)–C(3)–O(1)–P(1) ring in fragments A and B adopts an envelope conformation and the deviation of the P(1) atom from the plane of the rest of the atoms of this ring is −0.19 (A) and −0.21 Å (B).

The C(5)···C(10) ring has a distorted boat conformation. The C(7) and C(8) atoms are displaced out of the plane of other ring atoms by −0.62 and −1.03 Å, respectively. Fragment B adopts a half-chair conformation and deviations of the C(7′) and C(8′) atoms from the plane of other atoms of this ring are −0.40 and 0.37 Å. The difference in conformations of the C(5)···C(10) ring in fragments A and B can be attributed to the existence of shortened intermolecular contacts with participation of the ring atoms in B: H(6′A)···Cl′(1′) $(-1-x, -0.5+y, -0.5-z)$ 2.89 Å (the sum of the van der Waals radii [14] is 3.06 Å), H(7′B)···Cl′(1′) $(-1-x, -0.5+y, -0.5-z)$ 2.99 Å.

The C(8)···C(14) saturated ring has a chair-like conformation. The C(9) and C(13) atoms are displaced out of the plane of rest ring atoms by 0.61 (A), −0.67 Å (B), and −0.73 (A), 0.67 Å (B), respectively. Perhaps,

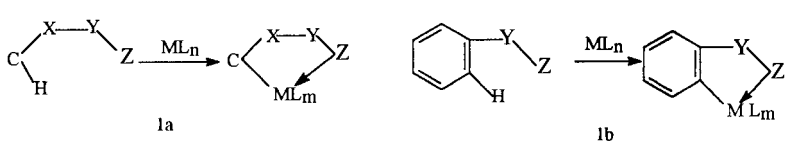

Fig. 1.

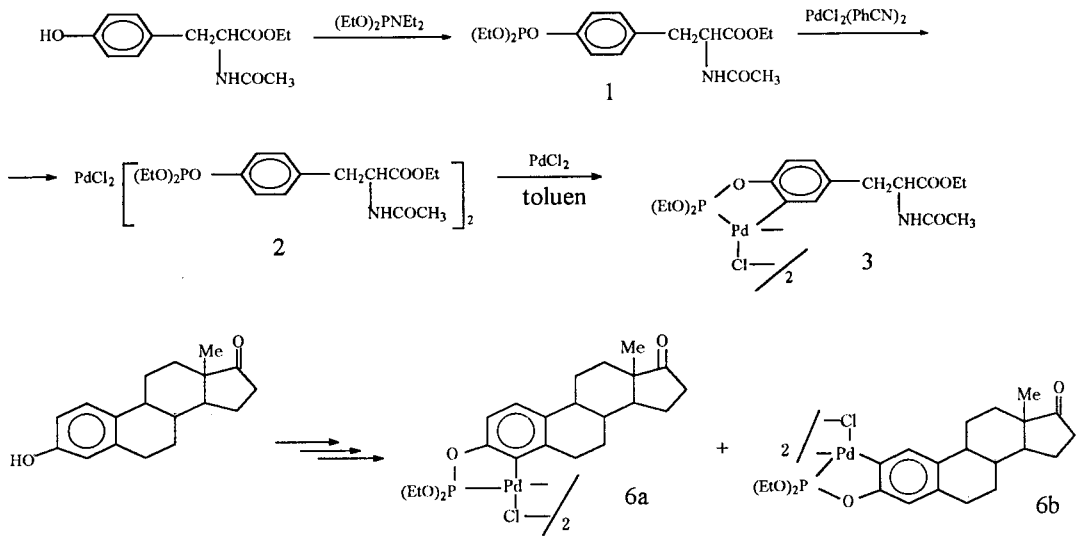

Fig. 2.

such conformations of these rings give rise to shortened intramolecular contacts: C(1)···H(11B) 2.81 Å (2.87 Å) (A), 2.71 Å (B), C(1)···H(11A) 2.79 Å (A), H(1)···C(11) 2.54 Å (A), 2.65 Å (B), H(1)···H(11A) 2.24 Å (2.32 Å) (A), 2.10 Å (B), C(11)···H(18C) 2.73 Å (A), 2.78 Å (B), H(11B)···C(18) 2.78 Å.

The C(13)···C(17) saturated five-membered ring adopts an envelope conformation and the deviation of the C(14) atom from the plane of the rest of the atoms of the ring is 0.61 (A) and −0.64 Å (B), respectively.

The C(18)H_3 methyl group has an axial orientation (the C(18)–C(13)–C(17)–C(16) torsion angles are 90(1) (A) and 87(1)° (B), respectively). Such an arrangement of these groups leads to the appearance of the shortened intramolecular contacts: C(15)···H(18A) 2.67 Å (A), 2.60 ((B), Å (15B)···C(18) 2.83 Å (A), 2.81 Å (B), H(15B)···H(18A) 2.24 Å (A), 2.18 Å (B), C(16)···H(18A) 2.83 Å (A), 2.79 Å (B).

The O(2)Et and O(3′)Et ethoxygroups have an axial orientation (the O(2)–P(1)–O(1)–C(3) and O(3′)–P(1′)–O(1′)–C(3′) torsion angles are −116.1(9) and 120.0(8)°) while the O(3)Et and O(2′)Et groups have equatorial orientations (the O(3)–P(1)–O(1)–C(3) and O(2)′–P(1′)–O(1′)–C(3′) torsion angles are 137.1(8) and −141.0(7)°, respectively).

The ethyl group at the O(3) atom is disordered and the occupation of the two sites is 0.5. The C(19)–C(20) and C(21′)–C(22′) ethyl groups have an antiperiplanar conformation (the P(1)–O(2)–C(19)–C(20) and P(1′)–O(3′)–C(21′)–C(22′) torsion angles are −170(2) and 169(1)°) while C(19′)–C(20′) group has an anticlinalic one (the P(1′)–O(2′)–C(19′)–C(20′) torsion angle is 139(1)°). In a disordered ethyl group, the C(21)–C(22) part has an anticlinalic conformation and the C(21A)–C(22A) part has a synclinalic one (the P(1)–O(3)–C(21)–C(22) and P(1)–O(3)–C(21A)–C(22A) torsion angles are −121(2) and 88(2)°, respectively).

3. Conclusions

It has been demonstrated that the hydroxy group in phenols can be used as a directing group for cyclopalladation after being converted into a mixed dialkoxy-O-phosphite ester. Corresponding optically active cyclopalladated compounds have been obtained from protected L-(+)-tyrosine and (+)-estrone. These enantiomeric compounds have a good scope for being asymmetric catalysts in terms of recent work by Bedford et al. [15]. The molecular structure of the latter has been determined using an X-ray method. This novel approach can obviously have a general applicability to phenol and some alcohols.

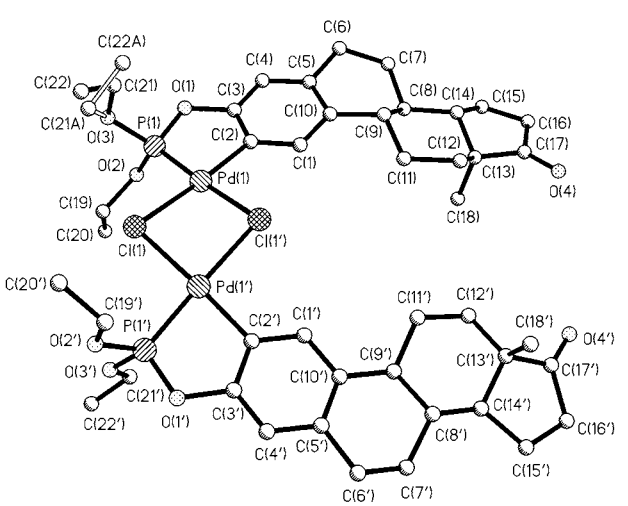

Fig. 3.

Table 1
Atomic coordinates of non H-atoms ($\times 10^4$) and isotropic thermal parameters of these atoms ($\times 10^3$) for compound **6b**

	x	y	z	U_{eq} (Å^2)
Pd(1)	−7554(1)	482(1)	−996(1)	42(1)
Pd(1′)	−6390(1)	−1787(1)	−1216(1)	43(1)
Cl(1)	−6752(4)	−899(2)	−618(1)	66(1)
Cl(1′)	−6315(3)	−230(2)	−1528(1)	44(1)
P(1′)	−6348(3)	−3221(2)	−955(1)	57(1)
P(1)	−8682(4)	1193(2)	−535(1)	60(1)
O(1)	−9101(9)	2251(6)	−674(2)	64(2)
O(1′)	−5977(8)	−3978(5)	−1287(2)	57(2)
O(2′)	−5284(8)	−3464(6)	−623(2)	82(3)
O(2)	−10 150(7)	809(7)	−415(3)	100(4)
O(3′)	−7617(9)	−3603(7)	−718(3)	106(4)
O(3)	−7932(9)	1364(7)	−132(2)	90(3)
O(4′)	−7522(10)	−697(5)	−4117(2)	69(2)
O(4)	−8284(13)	2761(8)	−3799(3)	102(4)
C(1′)	−6354(10)	−2209(6)	−2079(2)	33(2)
C(1)	−7979(9)	1834(7)	−1680(3)	39(2)
C(2)	−8185(10)	1684(7)	−1285(3)	45(2)
C(2′)	−6209(10)	−2585(7)	−1707(3)	40(2)
C(3′)	−6059(10)	−3576(7)	−1671(3)	43(2)
C(3)	−8851(12)	2415(7)	−1079(2)	52(3)
C(4)	−9176(11)	3286(8)	−1235(3)	53(3)
C(4′)	−5994(10)	−4171(6)	−1983(3)	41(2)
C(5′)	−6100(10)	−3807(7)	−2360(3)	42(2)
C(5)	−8920(11)	3451(6)	−1623(3)	48(3)
C(6′)	−5992(10)	−4495(7)	−2701(3)	42(2)
C(6)	−9190(12)	4432(7)	−1796(4)	56(3)
C(7′)	−6733(11)	−4105(6)	−3063(3)	45(2)
C(7)	−9486(14)	4455(7)	−2229(4)	66(3)
C(8′)	−6277(10)	−3067(6)	−3152(2)	34(2)
C(8)	−9302(11)	3505(7)	−2450(3)	45(2)
C(9′)	−6721(10)	−2404(6)	−2807(3)	40(2)
C(9)	−8055(10)	2938(6)	−2281(3)	38(2)
C(10′)	−6354(10)	−2808(6)	−2412(3)	37(2)
C(10)	−8323(9)	2724(6)	−1854(3)	39(2)
C(11′)	−6308(12)	−1342(6)	−2879(3)	45(2)
C(11)	−7677(13)	2031(7)	−2519(3)	50(3)
C(12′)	−6822(12)	−967(7)	−3275(3)	49(3)
C(12)	−7535(13)	2250(7)	−2961(3)	50(2)
C(13′)	−6385(11)	−1627(6)	−3604(3)	39(2)
C(13)	−8868(12)	2743(7)	−3115(3)	49(3)
C(14)	−9087(10)	3672(7)	−2889(3)	44(2)
C(14′)	−6856(10)	−2663(7)	−3524(3)	42(2)
C(15′)	−6679(11)	−3191(7)	−3916(2)	46(2)
C(15)	−10 129(13)	4234(8)	−3119(4)	66(3)
C(16′)	−7164(14)	−2441(8)	−4209(3)	60(3)
C(16)	−9727(14)	4060(8)	−3523(3)	63(3)
C(17′)	−7095(11)	−1464(8)	−3998(3)	51(3)
C(17)	−8858(13)	3132(8)	−3513(3)	59(3)
C(18′)	−4861(10)	−1539(7)	−3691(3)	48(2)
C(18)	−10 126(14)	2058(8)	−3094(4)	67(4)
C(19′)	−3873(9)	−3213(11)	−686(5)	90(5)
C(19)	−10 340(22)	−112(15)	−226(7)	153(11)
C(20)	−11 854(24)	−250(22)	−239(7)	184(13)
C(20′)	−3283(30)	−2819(20)	−323(6)	194(13)
C(21′)	−9007(14)	−3490(18)	−847(7)	161(11)
C(21)	−6552(13)	1718(20)	−159(9)	83(9)
C(21A)	−6550(12)	1133(18)	−23(10)	98(10)
C(22′)	−9889(18)	−4112(18)	−592(7)	147(9)
C(22)	−5365(30)	1149(22)	15(9)	92(9)
C(22A)	−6224(27)	2124(15)	−188(7)	58(6)

4. Experimental

N-acetyl-L-tyrosine ethyl ester and (+)-estrone were purchased from Aldrich. All reactions were carried out under argon. Optical rotations were measured with an EPO 1 instrument (Moscow Production), while NMR spectra were performed with a Bruker AMX-400 spectrophotometer.

*4.1. (+)-O-Diethoxyphosphino-[N-acetyl-L-tyrosine]ethyl ester (**1**)*

A 0.5 g (1.99 mM) sample of *N*-acetyl-L-tyrosine ethyl ester ($[\alpha]_D$ +24.0°, EtOH, *c* 1.0) and 0.482 g (2.5 mM) of $(EtO)_2PNEt_2$ was heated on an oil bath at 100°C under argon without solvent for 5 h and then other 5 h in vacuo to remove volatile substances. The residue was then dissolved in absolute Et_2O and filtered. After evaporation the weight of the dried product was 0.734 g (99%). $[\alpha]_D$ +53.7° (CH_2Cl_2, *c* 1.49). Found: C, 54.87; H, 7.05; P, 8.22; N, 3.72. $C_{17}H_{26}NO_6P$ Calc.: C, 54.99; H, 7.06; P, 8.35; N, 3.77%. ^{1}H-NMR ($CDCl_3$, ppm): 1.25 (t, 3H, $COOCH_2\underline{CH_3}$), 1.31 (t, 6H, $(\underline{CH_3}CH_2O)_2P$), 2.0 (s, 3H, $COCH_3$), 3.0–3.12 (m, 2H, CH_2Ph), 4.2 (q, 2H, $COO\underline{CH_2}CH_3$), 4.05 (q, 4H, $(CH_3\underline{CH_2}O)_2P$, 4.8 (m, 1H, $CH_2C\underline{H}$), 6.0 (d, 1H, $J = 7.6$ Hz, NH), 6.96–7.05 (m, 4H, C_6H_4). ^{31}P-NMR ($CDCl_3$, ppm): 134.23.

*4.2. Bis-{(+)-O-Diethoxyphosphino-[N-acetyl-L-tyrosine] ethyl ester}palladium dichloride (**2**)*

To 0.156 g (0.41 mM) of $PdCl_2(PhCN)_2$ in 10 ml of CH_2Cl_2 was added 0.316 g (0.85 mM) of **2** in 15 ml CH_2Cl_2. After stirring for 30 min, 100 ml of pentane or heptane was added. After the usual work-up the product weighted 0.345 g (90%). $[\alpha]_D$ +46.15° (CH_2Cl_2, *c* 0.53), m.p. 57°C. Found: C, 44.23; H, 5.74; N, 2.95; Cl, 7.73. $C_{34}H_{52}N_2O_{12}P_2PdCl_2$ Calc.: C, 44.38; H, 5.70; N, 3.07; Cl, 7.72%. ^{1}H-NMR (C_6D_6, ppm): 1.0 (t, 3H, $COOCH_2\underline{CH_3}$), 1.2 (t, 6H, $(\underline{CH_3}CH_2O)_2P$), 1.8 (s, 3H, $COCH_3$), 2.95–3.15 (m, 2H, CH_2Ph), 4.0 (q, 2H, $COO\underline{CH_2}CH_3$), 4.2 (m, 4H, $(CH_3\underline{CH_2}O)_2P$), 4.85 (m, 1H, $CH_2C\underline{H}$), 6.48 (d, 1H, $J = 7.8$ Hz, NH), 7.09–7.19 (m, 4H, C_6H_4). ^{31}P-NMR (C_6D_6, ppm): 89.7.

*4.3. (+)-{O-Diethoxyphosphino-P,3C-[N-acetyl-L-tyrosine] ethyl ester}palladiochloride dimer (**3**)*

To 0.5575 g (0.63 mM) of **2** ($[\alpha]_D$ +39.5°) suspended in toluene (30 ml) 0.13 g (0.73 mM) of $PdCl_2$ was added, and the mixture was heated under argon on an oil bath for 12 h. Progress of the reaction was monitored by the presence of HCl in outgoing gases. After cooling, the reaction mixture was filtered and evaporated to dryness. The product was transferred into

CH_2Cl_2 (10 ml) and 60 ml of heptane was added. The yellow precipitate was collected and dried in vacuo to afford 0.519 g (92.3%) of **3**, $[\alpha]_D$ +33.1° (CH_2Cl_2, *c* 0.544). Found: C, 39.56; H, 4.91; Cl, 7.06; P, 5.90. $C_{17}H_{25}NO_6ClPPd$ Calc.: C, 39.85; H, 4.92; Cl, 6.93; P, 6.05%. ^{1}H-NMR ($CDCl_3$, ppm): 1.21 (t, 3H, $COOCH_2\underline{CH_3}$), 1.35 (t, 6H, $(\underline{CH_3}CH_2O)_2P$), 1.95 (s, 3H, $COCH_3$), 2.8–3.0 (m, 2H, CH_2Ph), 4.02 (q, 2H, $COO\underline{CH_2}CH_3$), 4.14–4.24 (q, 4H, $(CH_3\underline{CH_2}O)_2P$), 4.7 (m, 1H, $CH_2\underline{CH}$), 6.0 (bs, 1H, NH), 6.55–6.85 (m, 3H, C_6H_3). ^{31}P-NMR ($CDCl_3$, ppm): 129.68.

4.4. O-Diethoxyphosphino-(+)-estrone (4)

A 0.29 g (1.07 mM) sample of (+)-estrone ($[\alpha]_D$ +145.4°, CH_2Cl_2 *c* 0.74) and 0.39 ml (excess) of $(EtO)_2PNEt_2$ was kept under argon in boiling acetonitrile for 6 h and then the solvent was evaporated and the residue was heated in vacuo for a further 3 h. After cooling, the product was transferred into ether from which 0.411 g (98%) of white solid was obtained, $[\alpha]_D$ +113.2° (CH_2Cl_2, *c* 2.29), m.p. 52°C. Found: C, 67.80; H, 8.09; P, 7.59. $C_{22}H_{31}O_4P$ Calc.: C, 67.67; H, 8.00; P, 7.94%. ^{1}H-NMR ($CDCl_3$, ppm): 0.86 (s, 3H, CH_3), 1.21–2.81 (m, 21H, alk. H), 3.97 (q, 4H, $(CH_3C\underline{H_2}O)_2P$), 6.76–7.18 (m, 3H, C_6H_3). ^{31}P-NMR (C_6D_6, ppm): 134.03.

Table 2
Selected bond lengths (Å) in compound **6b**

Pd(1)–C(2)	2.028(10)	C(5)–C(10)	1.405(13)
Pd(1)–P(1)	2.160(3)	C(5)–C(6)	1.501(13)
Pd(1)–Cl(1′)	2.399(2)	C(6′)–C(7′)	1.534(14)
Pd(1)–Cl(1)	2.434(3)	C(6)–C(7)	1.52(2)
Pd(1′)–C(2′)	2.023(9)	C(7′)–C(8′)	1.530(11)
Pd(1′)–P(1′)	2.173(3)	C(7)–C(8)	1.525(14)
Pd(1′)–Cl(1′)	2.402(2)	C(8′)–C(14′)	1.503(13)
Pd(1′)–Cl(1)	2.418(3)	C(8′)–C(9′)	1.558(11)
P(1′)–O(3′)	1.569(5)	C(8)–C(14)	1.540(14)
P(1′)–O(2′)	1.577(5)	C(8)–C(9)	1.555(13)
P(1′)–O(1′)	1.587(7)	C(9′)–C(10′)	1.509(13)
P(1)–O(2)	1.576(5)	C(9′)–C(11′)	1.540(12)
P(1)–O(3)	1.580(5)	C(9)–C(10)	1.518(13)
P(1)–O(1)	1.590(8)	C(9)–C(11)	1.539(12)
O(1)–C(3)	1.4296(11)	C(11′)–C(12′)	1.540(13)
O(1′)–C(3′)	1.434(11)	C(11)–C(12)	1.555(13)
O(4′)–C(17′)	1.207(12)	C(12′)–C(13′)	1.511(13)
O(4)–C(17)	1.24(2)	C(12)–C(13)	1.55(2)
C(1′)–C(2′)	1.385(12)	C(13′)–C(18′)	1.515(14)
C(1′)–C(10′)	1.410(12)	C(13′)–C(14′)	1.527(12)
C(1)–C(2)	1.388(12)	C(13′)–C(17′)	1.537(14)
C(1)–C(10)	1.406(13)	C(13)–C(17)	1.47(2)
C(2)–C(3)	1.392(12)	C(13)–C(14)	1.513(14)
C(2′)–C(3′)	1.381(13)	C(13)–C(18)	1.55(2)
C(3′)–C(4′)	1.349(13)	C(14)–C(15)	1.500(14)
C(3)–C(4)	1.354(14)	C(14′)–C(15′)	1.541(12)
C(4)–C(5)	1.38(2)	C(15′)–C(16′)	1.518(14)
C(4′)–C(5′)	1.394(14)	C(15)–C(16)	1.46(2)
C(5′)–C(10′)	1.412(12)	C(16′)–C(17′)	1.531(14)
C(5′)–C(6′)	1.512(13)	C(16)–C(17)	1.53(2)

Table 3
Selected bond angles (°) in compound **6b**

C(2)–Pd(1)–P(1)	80.5(3)	C(8′)–C(7′)–C(6′)	110.7(8)
C(2)–Pd(1)–Cl(1′)	96.5(2)	C(6)–C(7)–C(8)	116.6(9)
P(1)–Pd(1)–Cl(1′)	176.94(10)	C(14′)–C(8′)–C(7′)	114.0(8)
C(2)–Pd(1)–Cl(1)	176.7(3)	C(14′)–C(8′)–C(9′)	108.9(7)
P(1)–Pd(1)–Cl(1)	97.33(11)	C(7′)–C(8′)–C(9′)	108.6(7)
Cl(1′)–Pd(1)–Cl(1)	85.66(9)	C(7)–C(8)–C(14)	112.0(8)
C(2′)–Pd(1′)–P(1′)	81.2(3)	C(7)–C(8)–C(9)	109.8(9)
C(2′)–Pd(1′)–Cl(1′)	96.5(3)	C(14)–C(8)–C(9)	109.5(8)
P(1′)–Pd(1′)–Cl(1′)	176.47(10)	C(10′)–C(9′)–C(11′)	115.7(8)
C(2′)–Pd(1′)–Cl(1)	175.9(3)	C(10′)–C(9′)–C(8′)	113.7(7)
P(1′)–Pd(1′)–Cl(1)	96.57(10)	C(11′)–C(9′)–C(8′)	111.4(7)
Cl(1′)–Pd(1′)–Cl(1)	85.94(9)	C(10)–C(9)–C(11)	113.2(7)
Pd(1′)–Cl(1)–Pd(1)	89.46(8)	C(10)–C(9)–C(8)	108.9(8)
Pd(1)–Cl(1′)–Pd(1′)	90.69(8)	C(11)–C(9)–C(8)	113.4(8)
O(3′)–P(1′)–O(2′)	93.9(5)	C(1′)–C(10′)–C(5′)	118.1(8)
O(3′)–P(1′)–O(1′)	109.3(5)	C(1′)–C(10′)–C(9′)	120.8(7)
O(2′)–P(1′)–O(1′)	103.4(5)	C(5′)–C(10′)–C(9′)	120.9(8)
O(3′)–P(1′)–Pd(1′)	120.3(4)	C(5)–C(10)–C(1)	118.8(9)
O(2′)–P(1′)–Pd(1′)	120.3(4)	C(5)–C(10)–C(9)	118.5(8)
O(1′)–P(1′)–Pd(1′)	107.9(3)	C(1)–C(10)–C(9)	122.6(8)
O(2)–P(1)–O(3)	103.9(6)	C(12′)–C(11′)–C(9′)	112.2(8)
O(2)–P(1)–O(1)	98.9(5)	C(9)–C(11)–C(12)	112.4(8)
O(3)–P(1)–O(1)	104.1(5)	C(13′)–C(12′)–C(11′)	111.6(8)
O(2)–P(1)–Pd(1)	119.8(4)	C(11)–C(12)–C(13)	110.1(9)
O(3)–P(1)–Pd(1)	118.4(4)	C(12′)–C(13′)–C(18′)	111.9(9)
O(1)–P(1)–Pd(1)	109.1(3)	C(12′)–C(13′)–C(14′)	110.2(8)
C(3)–O(1)–P(1)	113.2(6)	C(18′)–C(13′)–C(14′)	113.8(8)
C(3′)–O(1′)–P(1′)	113.2(6)	C(12′)–C(13′)–C(17′)	116.4(8)
C(2′)–C(1′)–C(10′)	121.8(8)	C(18′)–C(13′)–C(17′)	104.6(8)
C(2)–C(1)–C(10)	120.8(9)	C(14′)–C(13′)–C(17′)	99.3(8)
C(1)–C(2)–C(3)	117.1(8)	C(17)–C(13)–C(14)	99.6(8)
C(1)–C(2)–Pd(1)	123.9(7)	C(17)–C(13)–C(18)	105.8(9)
C(3)–C(2)–Pd(1)	118.9(6)	C(14)–C(13)–C(18)	112.5(9)
C(3′)–C(2′)–C(1′)	117.7(9)	C(17)–C(13)–C(12)	118.1(10)
C(3′)–C(2′)–Pd(1′)	118.3(7)	C(14)–C(13)–C(12)	108.3(8)
C(1′)–C(2′)–Pd(1′)	123.8(7)	C(18)–C(13)–C(12)	112.0(8)
C(4′)–C(3′)–C(2′)	122.5(9)	C(15)–C(14)–C(13)	105.3(9)
C(4′)–C(3′)–O(1′)	119.4(9)	C(15)–C(14)–C(8)	120.0(9)
C(2′)–C(3′)–O(1′)	118.1(9)	C(13)–C(14)–C(8)	113.2(8)
C(4)–C(3)–C(2)	123.4(7)	C(8′)–C(14′)–C(13′)	112.9(7)
C(4)–C(3)–O(1)	119.0(8)	C(8′)–C(14′)–C(15′)	121.7(8)
C(2)–C(3)–O(1)	117.3(8)	C(13′)–C(14′)–C(15′)	104.6(8)
C(3)–C(4)–C(5)	119.3(9)	C(16′)–C(15′)–C(14′)	102.9(8)
C(3′)–C(4′)–C(5′)	120.9(8)	C(16)–C(15)–C(14)	103.5(10)
C(4′)–C(5′)–C(10′)	118.8(9)	C(15′)–C(16′)–C(17′)	105.9(8)
C(4′)–C(5′)–C(6′)	119.3(8)	C(15)–C(16)–C(17)	105.2(9)
C(10′)–C(5′)–C(6′)	121.9(9)	O(4′)–C(17′)–C(16′)	126.8(10)
C(4)–C(5)–C(10)	120.3(9)	O(4′)–C(17′)–C(13′)	125.3(9)
C(4)–C(5)–C(6)	120.1(9)	C(16′)–C(17′)–C(13′)	107.9(8)
C(10)–C(5)–C(6)	119.5(10)	O(4)–C(17)–C(13)	126.1(11)
C(5′)–C(6′)–C(7′)	112.0(7)	O(4)–C(17)–C(16)	125.0(10)
C(5)–C(6)–C(7)	116.1(9)	C(13)–C(17)–C(16)	108.9(10)

4.5. Bis-[O-diethoxyphosphino-(+)-estrone]palladium dichloride (5)

A total of 0.3427 g of **4** and 0.17 g of $PdCl_2(PhCN)_2$ was heated in CH_2Cl_2 for 1 h, then heptane was added

and the yellow precipitate was collected, giving 0.3995 g (95%) of **5**, $[\alpha]_D$ +85.5° (CH_2Cl_2, *c* 0.5), m.p. 112°C. Found: C, 55.05; H, 6.40; P, 6.18. $C_{44}H_{62}O_8P_2PdCl_2$ Calc.: C, 55.4; H, 6.52; P, 6.47%. ^{1}H-NMR (CD_2Cl_2, ppm): 0.8 (s, 3H, CH_3), 1.0–2.75 (m, 21H, alk. H), 4.16 (q, 4H, $(CH_3C\underline{H}_2O)_2P$), 6.81–7.16 (m, 3H, C_6H_3). ^{31}P-NMR (CD_2Cl_2, ppm): 89.71.

4.6. 1-Palladiochloride[O-diethoxyphosphino-(+)-estrone] dimer (**6a**) and 3-palladio-chloride[O-diethoxyphosphino-(+)-estrone] dimer (**6b**)

To 0.3404 g (0.36 mM) of **5** ($[\alpha]_D$ +85.5°) suspended in toluene (25 ml) 0.075 g (0.42 mM) of $PdCl_2$ was added, and the mixture was heated under argon on an oil bath for 12 h. Progress of the reaction was monitored by the presence of HCl in outgoing gases. After cooling, the reaction mixture was filtered and evaporated to dryness. After crystallization of **6a** and **6b** (total yield 90%) from the mixture in CH_2Cl_2:heptane, **6b** was obtained in pure form. $[\alpha]_D$ +150.4° (CH_2Cl_2, c 0.85), m.p. 185°C (dec.). Found: C, 49.60; H, 5.68; P, 5.81. $C_{22}H_{30}O_4PPdCl$ Calc.: C, 49.73; H, 5.69; P, 5.83%. ^{1}H-NMR ($CDCl_3$, ppm): ^{1}H-NMR ($CDCl_3$, ppm): 0.84 (s, 3H, CH_3), 1.2–2.8 (m, 21H, alk. H), 4.2–4.6 (q, 4H, $(CH_3CH_2O)_2P$), 6.57 (m, 1H, C_6H_2), 7.5 (m, 1H, C_6H_2). ^{31}P-NMR ($CDCl_3$, ppm): 131.8.

4.7. X-ray structural investigation of **6b**

The crystals $C_{44}H_{60}C_{12}O_8P_2Pd_2$ are orthorhombic, $M_W = 1062.56$. At 153(2) K, $a = 9.715(2)$, $b = 13.802(4)$ and $c = 34.34(1)$ Å, $V = 4605(2)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $D_{calc.} = 1.533$ g cm^{-3}, crystal size 0.5 × 0.4 × 0.3 mm, $\mu = 1.016$ mm^{-1}, $F(000) = 2176$.

The intensity of 5911 independent reflections was measured on an automatic four-circle Siemens P3/PC diffractometer (graphite monochromated Mo–K_α radiation, $\theta/2\theta$ scan, $2\theta_{MAKC} = 55$).

The structure was solved by direct methods using the SHELXTL PLUS 5.02 package [16]. The positions of all the H-atoms were calculated and refined using a 'riding' model $U_{iso} = nU_{eq}$ of the carbon atom connected to the relevant H-atom (where $n = 1.5$ for methyl groups and $n = 1.2$ for other hydrogen atoms). Eleven restraints were used during refinement: O(1)–C(3) 1.430(1), O(2′)–C(19′) 1.430(1), O(3)–C(21) 1.430(1), O(3′)–C(21′) 1.430(1), O(3)–C(21A) 1.430(1), C(21)–C(22) 1.52(1), C(21A)–C22(A) 1.52(1), O(2)–P(1) 1.580(5), O(2′)–P(1′) 1.580(5), O(3)–P(1) 1.580(5), and O(3′)–P(1′) 1.580(5) Å. Full-matrix least-squares refinement against F^2 (528 parameters) in an anisotropic approximation using 5849 reflections was carried, resulting in $R_1 = 0.057$ (for 3708 reflections with $F > 4(F)$), $wR_2 = 0.149$, and $S = 0.91$. The final atomic coordinates are given in Table 1. Selected bond lengths and angles are listed in Tables 2 and 3.

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