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Chiral Steroidal Phosphines: Synthesis and Platinum Complexes

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Summary. The synthesis of novel 3- and 17-diphenylphosphino-androstane derivatives *via* homogeneous catalytic P-C coupling is described. The products were characterized by ^{1}H and ^{31}P NMR measurements. According to the NMR investigation of the $PtCl_2P_2$-type complexes, the steroidal phosphines are *trans*-coordinated with respect to the Pt-centre exclusively.

Keywords. Coupling reaction; Homogeneous catalysis; Phosphines; Pt Complexes; Steroids.

Introduction

Hundreds of phosphorus-containing ligands with different steric and electronic properties, shapes, and functionalities have already been tested in various asymmetric homogeneous catalytic reactions [1]. In addition to the most widely used chiral diphosphines, whose synthesis is mainly based on the application of simple, easily available chiral compounds [2], some tertiary phosphines and phosphites possessing biologically important skeletons have also been prepared.

Although the number of chiral phosphorus ligands containing naturally occurring cyclic moieties is rather limited, even among the first optically active ligands there are some menthol-based derivatives [3]. Chiral sugar derivatives are also of high interest for asymmetric catalysis [4]. Ribo- and xylofuranose-based bulky diphosphite ligands have been tested in copper-catalyzed addition of diethylzinc to cyclohexenone [5].

Since the steroidal skeleton provides a chiral backbone for the functionalization with diaryl- or dialkylphosphino groups, it can serve as a promising candidate for the synthesis of optically active tertiary phosphines. Surprisingly, very little work has been devoted to this field. A cholestane-based phosphorus ligand has been first reported by *Horner* [6]. Diphenyl-(cholest-5-en-3β-yl)-phosphine has been synthesized from cholesteryl bromide. The quaternary phosphonium salts of the ligand

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have been studied in electrochemical reduction, phosphine oxide cleavage, and hydrogenolysis with lithium aluminum hydride.

Gladiali et al. have published on the synthesis of (*R,R*)-*diocol* (2,3-O-(5′α-cholestan-3′,3′-ylidene)-2,3-dihydroxy-1,4-*bis*-(diphenylphosphino)-butane), a steroid-substituted *diop* (2,3-O-isopropylidene-2,3-dihydroxy-1,4-*bis*-(diphenylphosphino)-butane) analogue, and its use as a ligand in enantioselective rhodium-catalyzed hydroformylation [7]. Complete chemo- and regioselectivities towards the more branched aldehydes have been obtained, but the isolated products were racemic. Recently, 3α-diphenylphosphino-cholest-5-ene and 3β-dimethylphosphino-cholest-5-ene have been synthesized from the corresponding 3β-methanesulfonate and 3β-chloro derivatives in the presence of Ph_2PLi [8]. Their palladium and platinum complexes have been characterized.

One of the most attractive approaches to the synthesis of various tertiary phosphines is the palladium- or nickel-catalyzed P-C coupling of aryl halides/triflates with primary or secondary phosphines [9–11].

In this paper we describe the synthesis and characterization of novel 3- and 17-diphenylphosphino-androstane derivatives *via* a homogeneous P-C coupling reaction. To the best of our knowledge, this is the first application of this method for steroidal alkenyl halides or enol triflates as substrates. The coordinative properties of the new phosphines towards platinum is also discussed.

Results and Discussion

Synthesis of steroidal phosphines

17-Iodo-androst-16-ene (**1**), 17-iodo-6α-hydroxy-3α,5α-cycloandrost-16-ene (**2**), 17-iodo-4-aza-androst-16-en-3-one (**3**), 17-iodo-4-aza-4-methyl-androst-16-en-3-one (**4**), and 17-bromo-androsta-2,16-diene (**5**) (Fig. 1) were reacted with

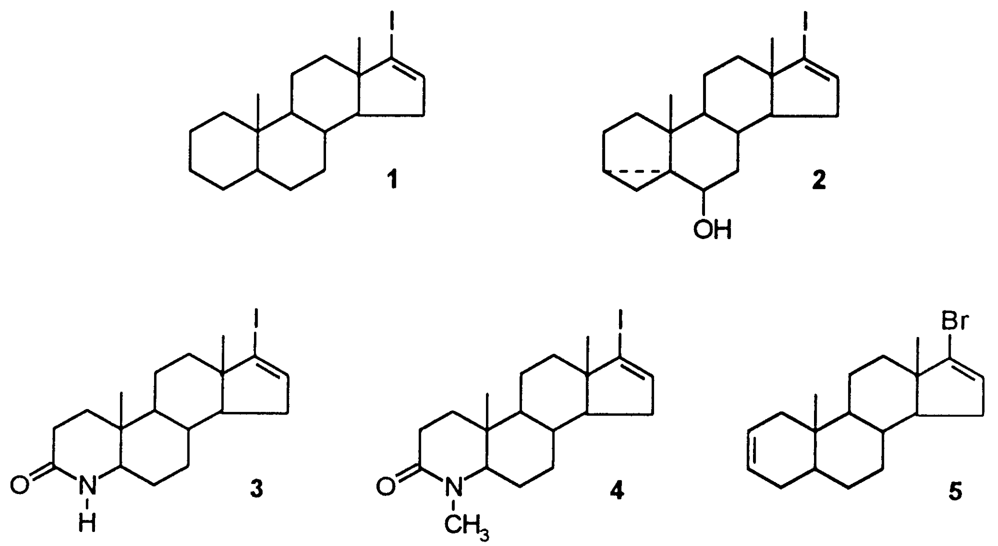
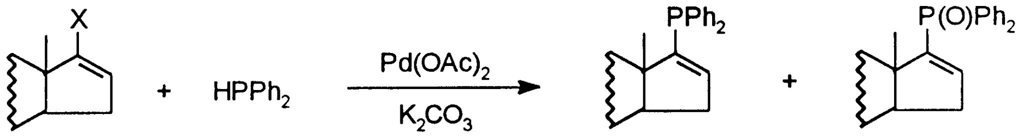


Fig. 1. Some steroidal substrates used in the coupling reaction



1: *X* = I	**1a**	**1b**
2: *X* = I	**2a**	**2b**
3: *X* = I	**3a**	**3b**
4: *X* = I	**4a**	**4b**
5: *X* = Br	**5a**	**5b**

Scheme 1

diphenylphosphine in the presence of palladium(II) acetate and a base (Scheme 1). As has been reported before by *Herd et al.* [11], the presence of a high amount of phosphine compared to that of the metal did not inhibit the reaction. At the same time, contrary to the results of the same group, the use of triethylamine as a base gave unsatisfactory results here. As has been observed in the *Heck* reaction of similar steroidal substrates before [12], the use of K_2CO_3 substantially improved the conversion.

The products were characterized by various spectroscopic methods (^{1}H and ^{31}P NMR, MS). Beside the desired products with the diphenylphosphino moiety, the presence of the corresponding phosphine oxides (7–10%) was observed in each case. These side products were formed both by oxidation of the phosphines and by coupling of the substrates with diphenylphosphine oxide, an impurity in the reagent.

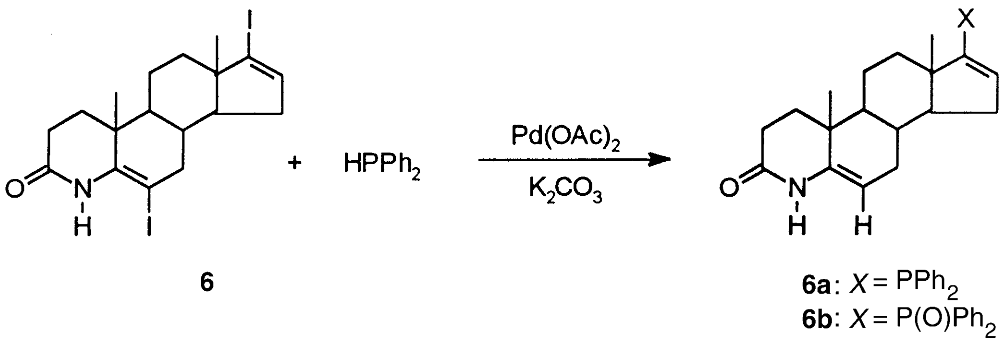
Whereas the substrates with the alkenyl iodide moiety (**1**–**4**) could be totally converted into the desired products in 2–5 hours (Table 1), the bromo derivative (**5**) reacted slowly, and **5a** was only produced in moderate yield (44%).

In the case of 6,17-diiodo-4-aza-androst-5,16-dien-3-one (**6**) (Scheme 2), the P-C coupling took place only at the 17-iodo-16-ene moiety, and a hydrodehalogenation occured at C-5. The different reactivity of the two iodo-alkenyl moieties of this

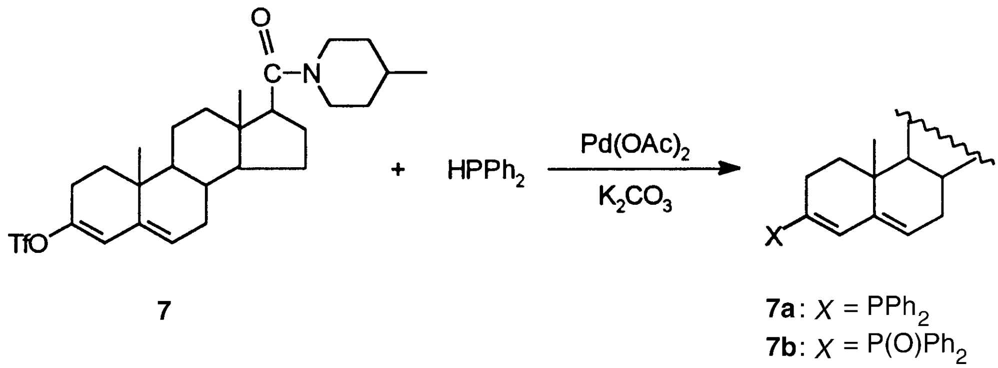
Table 1. Coupling reaction of steroidal substrates with $HPPh_2$[a]

Substrate	Reaction time / h	Product	Conversion[b] / %	Yield[b] / %
1	2	**1a**	99	92
2	2	**2a**	98	90
3	5	**3a**	96	87
4	3	**4a**	98	91
5	12	**5a**	44	34
6	2	**6a**	98	91
7	3	**7a**	89	80
8	2	**8a**	71	62

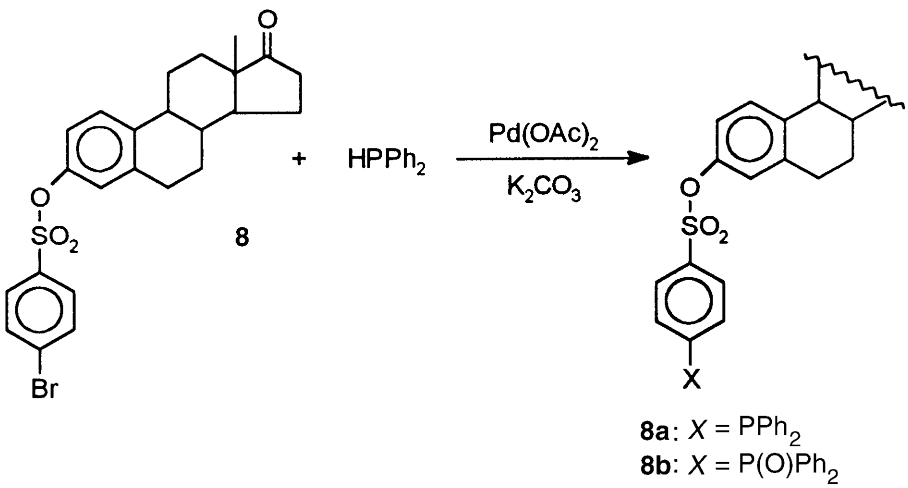
[a] Reaction conditions: substrate/$Pd(OAc)_2$/diphenylphosphine = 1/0.1/1, base: K_2CO_3, *DMF*, 90°C;
[b] determined by ^{1}H NMR from the reaction mixture



Scheme 2



Scheme 3



Scheme 4

substrate in some coupling reactions has been demonstrated before [13]. Under the reaction conditions used, hydrodehalogenation is a known side reaction. [14].

The reaction of 3-trifloxy-17β-(3′-methyl-pentan-1′,5′-diyl)-carboxamido-androsta-3,5-diene (**7**) also gave the corresponding tertiary phosphine in good yield (Scheme 3). Whereas the trifloxy group of **7**, however, could be easily substituted by

Table 2. ^{31}P NMR data of some steroidal phosphines and their platinum complexes

Phosphine	δ/ppm	Pt complex	δ/ppm	J(Pt-P)/Hz
1a	−24.3	*trans*-$PtCl_2$(**1a**)$_2$	10.0	2590
2a	−24.3	*trans*-$PtCl_2$(**2a**)$_2$	10.1	2586
4a	−24.2	*trans*-$PtCl_2$(**4a**)$_2$	10.1	2560
7a	−0.33	*trans*-$PtCl_2$(**7a**)$_2$	22.1	2605

the diphenylphosphino group, in the case of 3-(4′-bromo-phenyl-sulfonyloxy)-estra-1,3,5(10)-trien-17-one (**8**), **8a** was formed by substitution of the bromo moiety (Scheme 4). The same phenomenon has been observed before in the *Stille* coupling of this substrate [15].

Plantinum complexes of steroidal phosphines

For the exploitation of the above steroidal phosphines some preliminary investigations towards their coordination chemistry were carried out. The ^{31}P NMR spectra clearly proved the coordination of the phosphines to the Pt-center. Reacting **1a**, **2a**, **4a**, and **7a** with $PtCl_2(PhCN)_2$ in benzene [16] resulted in the formation of *trans*-$PtCl_2$(phosphine)$_2$ type complexes (Table 2) as expected [8]. The coupling constants of about 2500 Hz were of diagnostic value and showed the *trans*-disposition of the two phosphine moieties.

Experimental

General method for the synthesis of steroidal phosphines

In a typical experiment a mixture of 1 mmol steroidal alkenyl iodide, 0.01 mmol $Pd(OAc)_2$, 1 mmol K_2CO_3, and 1 mmol diphenylphosphine was heated under Ar in 5 cm^3 *DMF* at 90°C for 2–12 h. The reaction was monitored by TLC. After completion of the reaction the solvent was removed *in vacuo*. The residue was dissolved in toluene and filtered through Al_2O_3 under Ar. Evaporation of the solvent afforded the products.

^1H and ^{31}P NMR spectra were recorded at room temperature with a Varian Inova 400 NMR spectrometer at 400 and 161.92 MHz. GC-MS measurements (EI) were performed with a Hewlett-Packard 5971A GC-MSD instrument using a HP-1 column.

17-Diphenylphosphino-androst-16-ene (**1a**; $C_{31}H_{39}P$)

^1H NMR ($CDCl_3$, δ, 400 MHz): 7.6-7.3 (m, 10H, Ph), 5.4 (m, 1H, 16-H), 2.6-1.0 (m, 22H, ring protons), 0.95 (s, 3H, 18-H_3), 0.78 (s, 3H, 19-H_3) ppm; ^{31}P NMR ($CDCl_3$, δ, 161.92 MHz): −24.3 ppm; MS: *m/z* (rel.int.) = 442 (M^+) (100), 427 ppm; (M^+-CH_3) (68), 278 (60), 183 (23); yield: 85%.

17-Diphenylphosphino-6α-hydroxy-3α,5α-cycloandrost-16-ene (**2a**; $C_{31}H_{37}OP$)

^1H NMR ($CDCl_3$, δ, 400 MHz): 7.6-7.3 (m, 10H, Ph), 5.4 (m, 1H, 16-H), 3.22 (m, 1H, 6-H), 2.4-1.0 (m, 17H, ring protons), 1.00 (s, 3H, 18-H_3), 0.78 (s, 3H, 19-H_3), 0.42 (m, 1H, 4-H_a), 0.24 (m, 1H, 4-H_b) ppm; ^{31}P NMR ($CDCl_3$, δ, 161.92 MHz): −24.3 ppm; yield: 78%.

17-Diphenylphosphino-4-aza-androst-16-en-3-one (**3a**; $C_{30}H_{36}NOP$)

^{1}H NMR ($CDCl_3$, δ, 400 MHz): 7.6-7.3 (m, 10H, Ph), 5.65 (s, 1H, NH), 5.4 (m, 1H, 16-H), 3.05 (m, 1H, 5-H), 2.5-1.0 (m, 17H, ring protons), 0.92 (s, 3H, 18-H_3), 0.72 (s, 3H, 19-H_3) ppm; yield: 75%.

17-Diphenylphosphino-4-metil-4-aza-androst-16-en-3-one (**4a**; $C_{31}H_{38}NOP$)

^{1}H NMR ($CDCl_3$, δ, 400 MHz): 7.6-7.3 (m, 10H, Ph), 5.4 (m, 1H, 16-H), 3.05 (m, 1H, 5-H), 2.89 (s, 3H, N–CH_3), 2.5-1.0 (m, 17H, ring protons), 0.93 (s, 3H, 18-H_3), 0.72 (s, 3H, 19-H_3) ppm; ^{31}P NMR ($CDCl_3$, δ, 161.92 MHz): -24.2 ppm; yield: 78%.

17-Diphenylphosphino-androsta-2,16-diene (**5a**; $C_{31}H_{37}P$)

^{1}H NMR ($CDCl_3$, δ, 400 MHz): 7.6-7.3 (m, 10H, Ph), 5.55 (m, 2H, 2-H+3-H), 5.4 (m, 1H, 16-H), 2.6-1.0 (m, 18H, ring protons), 0.99 (s, 3H, 18-H_3), 0.75 (s, 3H, 19-H_3) ppm; yield: 24%.

17-Diphenylphosphino-4-aza-androsta-5,16-dien-3-one (**6a**; $C_{30}H_{34}NOP$)

^{1}H NMR ($CDCl_3$, δ, 400 MHz): 7.6-7.3 (m, 11H, Ph+NH), 5.40 (m, 1H, 16-H), 4.80 (m, 1H, 6-H), 2.6-1.3 (m, 15H, ring protons), 1.25 (s, 3H, 18-H_3), 1.08 (s, 3H, 19-H_3) ppm; yield: 78%.

3-Diphenylphosphino-17β-(3′-methyl-pentan-1′,5′-diyl)carboxamido-androsta-3,5-diene (**7a**; $C_{38}H_{48}NOP$)

^{1}H NMR ($CDCl_3$, δ, 400 MHz): 7.6-7.3 (m, 10H, Ph), 5.65 (m, 1H, 6-H), 5.38 (m, 1H, 4-H), 4.6-1.05 (m, 27H, ring protons), 0.91 (s, 3H, 18-H_3), 0.85 (s, 3H, 19-H_3), 0.72 (d, $J = 7$ Hz, 3H, 4′-CH_3) ppm; ^{31}P NMR ($CDCl_3$, δ, 161.92 MHz): -0.3 ppm; yield: 68%.

3-(4′-(Diphenylphosphino)-phenyl-sulfonyloxy)-estra-1,3,5(10)-trien-17-one (**8a**; $C_{36}H_{35}O_4PS$)

^{1}H NMR ($CDCl_3$, δ, 400 MHz): 7.6–7.3 (m, 10H, Ph), 7.66 (d, $J = 7$ Hz, 2H, 2′-H, 6′-H), 7.30 (d, $J = 7$ Hz, 2H, 3′-H, 5′-H), 7.18 (d, $J = 9$ Hz, 1H, 1-H), 6.79 (d, $J = 3$ Hz, 1H, 4-H), 6.68 (dd, $J = 9$ Hz, 3Hz, 1H, 2-H), 3.0-1.3 (m, 15H, ring protons), 0.85 (s, 3H, 18-H_3) ppm; ^{31}P NMR $CDCl_3$, δ, 161.92 MHz): -4.0 ppm; yield: 55%.

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