Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Molecular Catalysis A: Chemical 247 (2006) 275–282
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Selective hydrogenation of α,β-unsaturated oxosteroids with homogeneous rhodium catalysts

Rui M.D. Nunes [a], Andreia F. Peixoto [a], M. Rosa Axet [b], Mariette M. Pereira [a,*], Maria José Moreno [c], László Kollár [d], Carmen Claver [b], Sergio Castillón [b]

[a] *Departamento de Química, Universidade de Coimbra, Rua Larga, 3004-535 Coimbra, Portugal*
[b] *Facultad de Química, Universitat Rovira i Virgili, C/Marcelí Domingo s/n, 43007 Tarragona, Spain*
[c] *Centro de Estudos Farmacêuticos, Faculdade de Farmácia, Universidade de Coimbra, 3000-295 Coimbra, Portugal*
[d] *Department of Inorganic Chemistry, University of Pécs, Ifjúság u. 6., H-7623 Pécs, Hungary*

Received 20 October 2005; received in revised form 17 November 2005; accepted 18 November 2005
Available online 18 January 2006

Abstract

A comparative study of the ligand (**5**–**10**) effect on the rhodium catalytic activity and selectivity in the homogeneous hydrogenation of α,β-unsaturated oxosteroids (**1**–**4**) is reported. The highest activity for C=C reduction was observed with phosphite ligands, being diphosphite **10** the most active. Furthermore, the presence of phosphite **6** significantly enhances the chemo and α-diastereoselectivity for the hydrogenation reaction. The β-methyl groups of the steroidal framework lead to a very high α-diastereoselectivity, even in the absence of phosphorous ligands. Substrate **4** is the paradigm presenting higher than 94% α-diastereoselectivity for any catalytic system studied.

The catalytic system formed from rhodium and the new diphosphite **10** also revealed a remarkable tendency for the C=O reduction and a noteworthy stability.

Keywords: Hydrogenation; Steroid; Oxosteroid; Rhodium; Phosphine; Phosphite

1. Introduction

In steroid chemistry metal–ammonia solutions have been widely used for the reduction of conjugated enones and dienones [1,2]. Heterogeneous catalysis has also been extensively employed in steroid hydrogenation being palladium the preferred catalyst for the selective reduction of carbon–carbon double bonds of α,β-unsaturated ketones [1]. Although the homogeneous catalysts are quite effective for the hydrogenation of steroidal double bonds, less information is available in the literature related to the reduction of α,β-unsaturated oxosteroids. However, tuning of the reduction selectivity through the design of catalysts and reaction conditions makes homogeneous catalysis an attractive method. For instance, under these conditions the reduction of Δ^4-3-keto steroids gives mainly the 5α-isomer, while the heterogeneous catalysts produce essentially the 5β-isomer. This reversal of stereoselectivity can be of great utility and should be exploited in the synthesis of potential bioactive molecules. The application of homogeneous reduction of unsaturated oxosteroids using rhodium catalysts prepared in situ was described by Kollár et al. [3] where it was shown that the reaction conditions and ligand structure have a remarkable influence on the chemoselectivity and diastereoselectivity of the hydrogenation reaction [3].

In this paper we present a systematic study on the selectivity of the reduction of α,β-unsaturated oxosteroids **1**–**4** using in situ rhodium catalysts containing P-ligands. Systematic variation of the reaction conditions and ligands **5**–**10**, allows a convenient modulation of the chemo- and diastereoselectivity of the hydrogenation, contributing thereby to a better understanding of the reaction mechanism.

2. Experimental

2.1. Equipments and reagents

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on Bruker Avance 300 operating at 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C, Varian 400 spectrometer at 400.12 MHz for

* Corresponding author. Tel.: +351 239854474; fax: +351 239827703.
E-mail address: mmpereira@qui.uc.pt (M.M. Pereira).

1381-1169/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2005.11.058

^{1}H and 100.62 MHz for ^{13}C. TMS was used as internal reference. ^{1}H assignments were made using 2D *g*COSY and NOESY (mixing time of 1 s) experiments, while ^{13}C assignments were made using 2D *g*HSQC experiments. GC and GC–MS experiments were carried out on Agilent 6890 series equipped with capillary Agilent HP5 columns with 30 and 0.5 m, respectively.

Phosphine ligands 9,9-dimethyl-4,5-bis(diphenylphosphino) xanthene (**7**), 1,2-bis(diphenylphosphino)ethane (**8**) and triphenylphosphine (**5**) were purchased from Strem Chemicals and Merck. Ligand **9** was prepared following reported procedures [4], and ligand **10** [5] was prepared from 1,6-di-*O*-(*t*-butyldiphenylsilyl)-2,5-anhydro-D-mannitol [6,7] by reaction with 4,4′,6,6′-tetra-*t*-butyl-2,2′-bisphenoxyphosphorous chloride [4,8]. Tris-(*o*-tert-butylphenyl)phosphite (**6**) was prepared according to described procedures [9].

$[Rh_2(\mu\text{-}Cl)_2(cod)_2]$ and $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ [10] were synthesized accordingly to literature procedures.

Solvents were obtained from commercial sources (Aldrich) distilled and dried before use, according to standard procedures [11].

2.2. General hydrogenation procedure

A stock solution of the desired rhodium precursor (8.06×10^{-3} mmol) was prepared in a Schlenk vessel. Toluene (10 ml) was added and then purged. The appropriate amounts of substrate and ligand (see Tables 1–3) as well as a stirring bar were introduced in the autoclave. The system was closed and purged. The suitable volume of the rhodium precursor solution was introduced in the reactor through an inlet cannula. The reactor was then pressurized with hydrogen. After reaching the working temperature, stirring was initiated. The conversions and selectivities were determined by gas chromatography.

2.2.1. Reduction of 4-androstene-3,17-dione *1*

4-Androstene-3,17-dione **1** was submitted to catalytic hydrogenation according to the general procedure described above. The autoclave was charged with steroid **1** (200.13 mg, 0.70 mmol), ligand **6** (30.3 mg, 0.06 mmol), and $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ (6.0 mg, 2.7×10^{-2} mmol). Twenty milliliter of toluene was introduced in the autoclave via syringe and then

Table 1
Rhodium catalysed hydrogenation of steroid **1**

Entry	Ligand	Conversion (%)		Chemoselectivity (1 h)		Diastereoselectivity (1 h), **11**:**12**
		1 h	3 h	**11** + **12** (%)	Mixture of alcohols (%)	
1	No P	58	96	91	9	71:29
2[a]		43	93	75[b]	6	63:37
3[c]		16	28	84	16	67:33
4	**5**	53	76[d]	85	15	68:32
5[e]		73	99	76	24	73:27
6	**6**	84	98	98	2	80:20
7[c]		12	22	68	32	60:40
8	**7**	80	99	87	13	63:37
9	**8**	87	98	87	13	64:36
10	**9**	–	72	90	10	63:37
11	**10**	99	–	87	13	58:42
12		–	100	56	44	80:20[f]

Reaction conditions (unless otherwise stated): $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ (1.6×10^{-3} mmol), substrate:P:Rh = 25:2.5:1, P_{H_2} = 20 bar, T = 100 °C, solvent: toluene (2 ml).
[a] Solvent, CH_3CN.
[b] 19% Unidentified products.
[c] $[Rh_2(\mu\text{-}Cl)_2(cod)_2]$ used as precursor.
[d] Precipitation of Rh metal observed in the reaction vessel.
[e] Reaction in the presence of Et_3N.
[f] Reaction time, 3 h.

Table 2
Rhodium catalysed hydrogenation of steroid **2**

Entry	Ligand	Conversion (%)		Products (1 h)			Diastereoselectivity (1 h), **11**:**12**
		1 h	3 h	**1** (%)	**11** + **12** (%)	Alcohols (%)	
1	No P	83	100	2	90	8	76:24
2	**5**	82	100[a]	32	65	3	60:40
3	**6**	90	100	35[b]	59[b]	1[b]	76:24
4	**7**	80	100	4	89	7	61:39
5	**8**	67	99	5	84	11	72:28
6	**9**	76	99	36	59	5	58:42
7	**10**	100	–	16	73	11	67:33

Reaction conditions (unless otherwise stated): $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ (1.6×10^{-3} mmol), substrate:P:Rh = 25:2.5:1, P_{H_2} = 20 bar, T = 100 °C, solvent: toluene (2 ml).
[a] Precipitation of Rh metal was observed in the reaction vessel.
[b] 5% non-identified products.

Table 3
Rhodium catalysed hydrogenation of steroid **4**

Entry	Ligand	Conversion (%)		Chemoselectivity (1 h)		Diastereoselectivity (1 h), **19:20**
		1 h	3 h	**19** + **20** (%)	Byproducts (%)	
1	No P	37	73	99	1	98:2
2	**5**	45	85[a]	90	10	95:5
3	**6**	84	99	97	3	98:2
4	**7**	64	96	92	8	96:4
5	**8**	36	43	89	11	97:3
6	**9**	25	53	96	4	97:3
7	**10**	95	–	96	4	94:6

Reaction conditions (unless otherwise stated): $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ (1.6×10^{-3} mmol), substrate:P:Rh = 25:2.5:1, P_{H_2} = 20 bar, T = 100 °C, solvent: toluene (10 ml).
[a] Precipitation of Rh metal observed in the reaction vessel.

pressurized to 20 bar H_2 and heated to 100 °C. The reaction was maintained during 3 h. After this time, the catalytic reaction was stopped, the reactor was cooled and depressurized. Evaporation of toluene afforded a crude that was submitted to silica gel preparative column chromatography using CH_2Cl_2:AcOEt (9:1) as eluent. The major fraction was evaporated and the solid product recrystallized from petroleum ether yielding 114 mg (57%) of 5α-H-androstan-3,17-dione **11**.

MS-CI (PCI): *m/z* 288 (M^+, 100%), 270 (81%), 252 (10%), 146 (9%); ^{1}H NMR (400 MHz, ppm): δ = 0.82 (s, 3H, 18-Me); 0.99 (s, 3H, 19-Me); 1.48 (m, 1H, 5-CH); 2.40 (dd, 1H, J = 19.5 and 8.5 Hz, 4-CH$_2$); 1.30 (m, 6-CH$_2$); 1.21 (m, 7-CH$_2$); 1.86 (m, 7-CH$_2$); 1.57 (m, 8-CH); 1.25 (m, 9-CH); 1.34, 1.60 (m, 11-CH$_2$); 1.62 (m, 12-CH$_2$); 1.30 (m, 15-CH$_2$); 1.80 (dt, ^3J = 12.0 and 4.0 Hz, 15-CH$_2$); 1.99 (m, 16-CH$_2$), 2.63 (t, J = 9.3 Hz, 16-CH$_2$); ^{13}C NMR: δ = 37.1 (C2), 212.5 (C3), 26.3 (C7), 20.4 (C8), 24.7 (C11), 35.8 (C12), 31.6 (C15), 42.2 (C16), 220.9 (C17), 22.6 (C18), 13.8 (C19). $[\alpha]_D$ = +102.0° (*c* 1, CH_2Cl_2); mp: 130–132 °C, lit. [12] 132–133 °C; Anal. calcd. For $C_{19}H_{28}O_2$: C, 79.12; H, 9.78; Found C, 79.02; H, 9.42.

2.2.2. Reduction of 1,4-androstadiene-3,17-dione 2

1,4-Androstadiene-3,17-dione **2** was submitted to catalytic hydrogenation according to the general procedure described in Section 2.2.1. Evaporation of toluene afforded a crude that was submitted to silica gel preparative column chromatography using CH_2Cl_2:AcOEt (9:1) as eluent. The major fraction was evaporated and the solid product crystallized from petroleum ether yielding (53%) of 5α-H-androstan-3,17-dione **11**. All the characterization data is in agreement with compound **11**, previously described.

2.2.3. Reduction of 3β-acetoxypregna-5,16-dien-20-one 4

3β-Acetoxypregna-5,16-dien-20-one **4** was submitted to catalytic hydrogenation according to the procedure described in Section 2.2.1. After evaporation of toluene the crude was purified by silica gel preparative column chromatography using CH_2Cl_2:AcOEt (9:1) as eluent. The major fraction was evaporated and the solid product crystallized from petroleum ether yielding 80.1 mg (86%) of 3β-acetoxy-17α-H-pregn-5-ene **19**.

^{1}H NMR (300 MHz, ppm): δ = 0.63 (s, 3H, 18-Me); 1.03 (s, 3H, 19-Me); 2.52 (t, J = 9.0 Hz, 1H, 17-CH); 1.19, 1.87 (m, 1-CH$_2$); 1.59 (m, 2-CH$_2$); 4.60 (m, 1H, 3-CH); 2.30 (d, J = 4.8 Hz, 2H, 4-CH$_2$); 5.38 (d, J = 5.1 Hz, 1H, 6-CH$_2$); 1.47 (m, 7-CH$_2$); 1.99 (td, J = 5.0 and 2.0 Hz, 7-CH$_2$); 1.58 (m, 8-CH); 1.00 (m, 9-CH); 1.15 (m, 11-CH$_2$); 1.46 (m, 12-CH$_2$); 2.05 (m, 12-CH$_2$); 2.13 (s, 3H, 21-Me); 2.03 (s, 3H, 3β-acetate methyl); ^{13}C NMR: δ = 36.95 (C1), 20.98 (C2), 73.80 (C3), 38.02 (C4), 139.60 (C5), 122.30 (C6), 31.1 (C7), 31.76 (C8), 49.82 (C9), 36.55 (C10), 27.68 (C11), 43.94 (C13), 36.94 (C15), 22.76 (C16), 63.64 (C17), 209.57 (C20), 31.54 (C21), 170.54 (3β-acetate carbonyl), 21.41 (3β-acetate methyl). $[\alpha]_D$ = −4.17° (*c* 1, CH_2Cl_2); mp: 145–147 °C, lit. [13] 146–147 °C; Anal. calcd. For $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; Found C, 77.66; H, 9.39.

3. Results and discussion

4-Androstene-3,17-dione **1**, was selected as model substrate to study the chemoselectivity and the diastereoselectivity of C=C versus C=O reduction using a rhodium-modified catalyst. The evaluation of the ligand structure effect on the catalytic reaction was extended to the conjugated dienone **2** at ring A, as well as to the conjugated enone **3** at ring B and also to the exocyclic enone that contains an isolated Δ^5-double bond, the Δ^5,Δ^{16}-20-ketone **4** (Fig. 1).

In order to study the effect of ligand in the selectivity of the reaction we selected monophosphine **5** and monophosphite **6** ligands, as well as diphosphines **7** and **8** and diphosphites **9** and **10** (Fig. 2). Ligands **5**, **7** and **8** are commercially available, **6** [9] and **9** [4] were prepared following reported procedures. Ligand **10** was prepared [5] from 1,6-di-*o*-(*t*-butyldiphenylsilyl)-2,5-anhydro-(D)-mannitol [6,7] by reaction with 4,4′,6,6′-tetra-*t*-butyl-2,2′-bisphenoxyphosphorous chloride [4,8] (Scheme 1).

In a typical hydrogenation reaction the selected substrate (**1**–**4**), the desired phosphorous ligand (**5**–**10**) and the toluene solution of rhodium precursor were introduced in the autoclave. The autoclave was then pressurized with H_2 and the temperature raised to working temperature. The reaction was maintained with stirring at constant pressure for 3 h.

The effect of ligand structure **5**–**10** on the activity, chemoselectivity and diastereoselectivity of the reduction of 4-androstene-3,17-dione **1** is presented in Table 1.

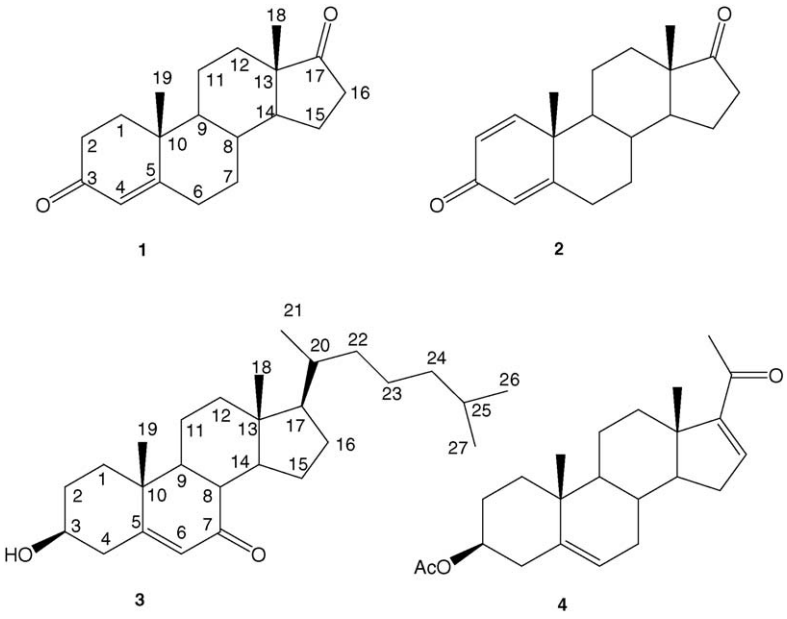


Fig. 1. Substrate structures.

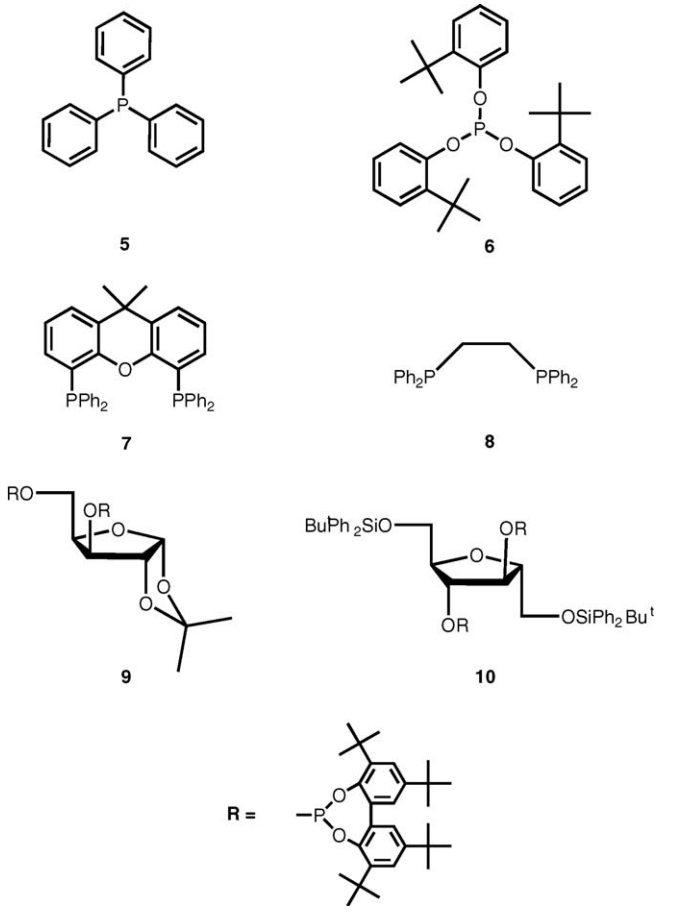
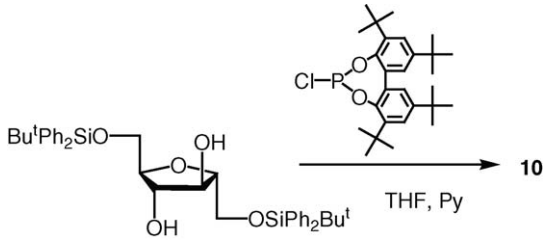


Fig. 2. Ligand structures.



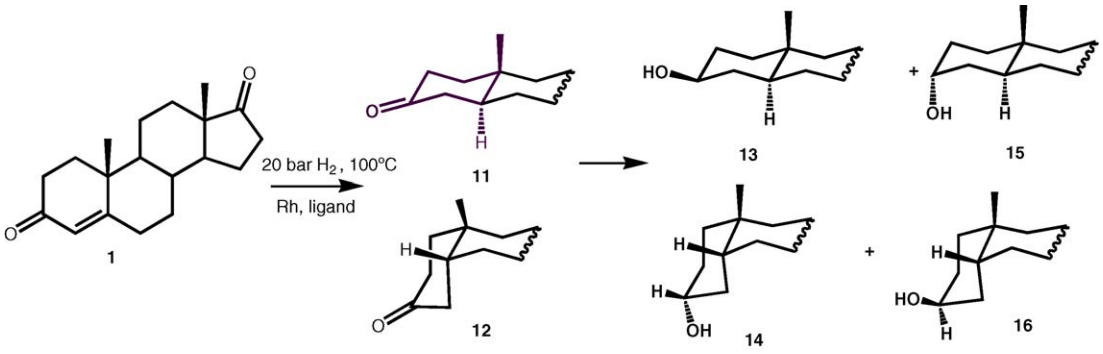
Scheme 1.

The product mixtures were analysed and the compounds **11**–**16** were identified, Scheme 2.

The catalytic activity is significantly dependent on the structure of the ligands coordinated to the rhodium and also on the catalytic precursor. The use of $[Rh_2(\mu\text{-}Cl)_2(cod)_2]$ instead of $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ strongly reduces the catalytic activity (Table 1, entries 3 and 7). An influence of the solvent was also observed, toluene affords 58% conversion after 1 h of reaction (Table 1, entry 1) while acetonitrile decreases the activity to 43% (Table 1, entry 2).

If the catalytic reaction is done in the presence of Et_3N a significant increase in the catalytic activity is observed (Table 1, entry 5). It is well documented that in the hydrogenation of C=C and C=O bonds with rhodium homogeneous catalysts two different mechanisms, involving the Rh(III) dihydride (hard Lewis acid) or Rh(I) monohydride (soft Lewis acid) active species can be involved [14–16] being the monohydrides the most active ones [17]. The presence of Et_3N in the reaction medium or of the strong base MeO^- in the catalytic precursor, may shift the equilibrium to the Rh(I) species and, consequently, the catalytic system becomes more active.

Furthermore, the catalytic activity is also increased by the presence of phosphite **6** and diphosphines **7** and **8** (Table 1, entries 6, 8 and 9) compared to blank (Table 1, entry 1). Among the reactions performed with phosphite ligands, the highest catalytic activity for this steroidal internal double bond reduction was reached with the new diphosphite **10**, 99% conversion after 1 h (Table 1, entry 11).



Scheme 2.

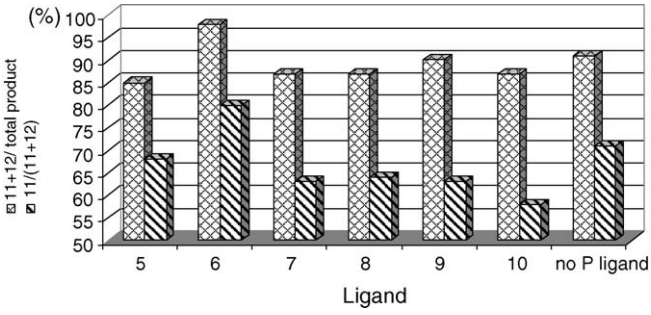


Fig. 3. The chemoselectivity and diastereoselectivity for the C=C hydrogenation of steroid **1** (1 h).

The relative chemoselectivities for C=C reductions of all the catalytic systems studied are presented in Fig. 3. The highest chemoselectivity was achieved using monophosphite **6** as ligand (Table 1, entry 6). In striking contrast, diphosphite **10** besides the highest activity in the reduction of C=C bond (Table 1, entry 11), also shows great activity in the reduction of the C=O groups (Table 1, entry 12) being especially significant the reduction of the conjugated carbonyl at C3. It should be emphasized that the catalytic system formed in the presence of ligand **10**, after longer reaction times (16 h), leads mainly to the reduction of the carbonyl groups (82%). This mixture of products obtained was characterized by NMR and GC–MS and is presented in Scheme 2. In spite of the different reactivity of **11** and **12**, both suffer further reduction mainly of the carbonyl at C3, leading to the preferential formation of the thermodynamically more stable equatorial alcohols **13** (40%) presenting ^{1}H NMR peak at $\delta = 3.55$ (m, 3-C<u>H</u>) with diaxial $^{3}J_{a,a}$ couplings and ^{13}C NMR at $\delta = 71.4$ (C3), and **14** (27%) with ^{1}H NMR peak at $\delta = 3.59$ (m, 3-C<u>H</u>) with diaxial $^{3}J_{a,a}$ couplings and ^{13}C NMR at $\delta = 70.9$ (C3). Together with the equatorial alcohols, smaller amounts of axial alcohols **15** (15%) showing ^{1}H NMR broad signal at $\delta = 4.05$, (bt, 3-C<u>H</u>) due to the lack of diaxial $^{3}J_{a,a}$ couplings and ^{13}C NMR peak at $\delta = 66.7$ (C3), and **16** (11%) with ^{1}H NMR at $\delta = 3.98$, (bt, 3-C<u>H</u>) broad signal due to the lack of diaxial $^{3}J_{a,a}$ couplings, ^{13}C NMR $\delta = 66.1$, were also observed.

In summary, for substrate **1**, phosphite **6** yields the highest chemoselectivity in the reduction of the Δ^4 double bond remaining the carbonyl groups at the C3 and C17 positions almost unaffected after 3 h of reaction.

The stability of the catalytic system rhodium-ligand **10** was also evaluated. A yellow coloured solution, typical of homogeneous catalytic species, was observed when the reactor was opened to the air after 16 h of reaction. Subsequent addition of more steroid **1** (20 mg) to this reaction mixture, maintaining the previously described experimental conditions, allowed further C=C reduction with activity and selectivity identical to the one presented in Table 1 (entry 11). Similar experiments were performed using ligand **6** but an extensive destruction of the catalyst to metallic rhodium was observed after 16 h of reaction, yielding isomeric alcohols (52%). These results emphasize that ligand **10** produces particularly stable homogeneous catalytic species even in the presence of air.

The NOESY spectrum of the isolated major product did not show any cross peaks between β-19 methyl group and H-5 proton, indicating that the two groups are on different faces of the steroidal plane, consequently the H-5 is in the α-face of steroid framework.

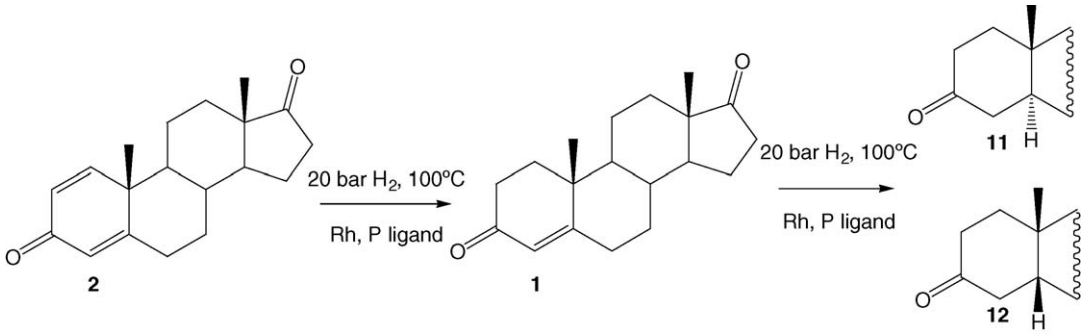
Diastereoselectivity for the reduction of the C=C bond on substrate **1** is presented in Fig. 3. For all the reactions performed, even in the absence of phosphorous ligands, the preferential formation of the 5α-isomer **11** was observed, pointing out the involvement of homogeneous catalytically active rhodium species [3,18–21].

The catalytic system using phosphite **6** resulted in the highest diastereoselectivity in the C=C reduction. The diphosphite **10** showed a particular behaviour also in this context, since 5-α and 5-β isomers **11** and **12**, present different reactivity for the carbonyl reduction at C3 (Table 1, entry 12). The diastereoselectivity increases along the reaction due to the preferential 3-keto group reduction of the β-isomer **12** (Table 1, entries 11 and 12), consequently the ratio **11**:**12** changes for longer reaction times.

Temperature dependence of the diastereoselectivity (50, 65 and 100 °C) was tested and no significant effect was observed.

Similar catalytic reaction conditions have been applied to the hydrogenation of androsta-1,4-diene-3,17-dione **2** possessing a conjugated dienone structure, Scheme 3, and catalytic results are presented in Table 2.

As previously observed, the catalytic activity is dependent on the ligand structure, being the highest activity observed for ligand **10** (Table 2, entry 7). For all the ligands studied, an almost complete conversion of the dienone **2** into the final saturated ketones **11** and **12** was obtained through the intermediate



Scheme 3.

α,β-unsaturated ketone **1**. This result is explained by the easier approach of the catalytically active species to the sterically less hindered Δ^1 double bond.

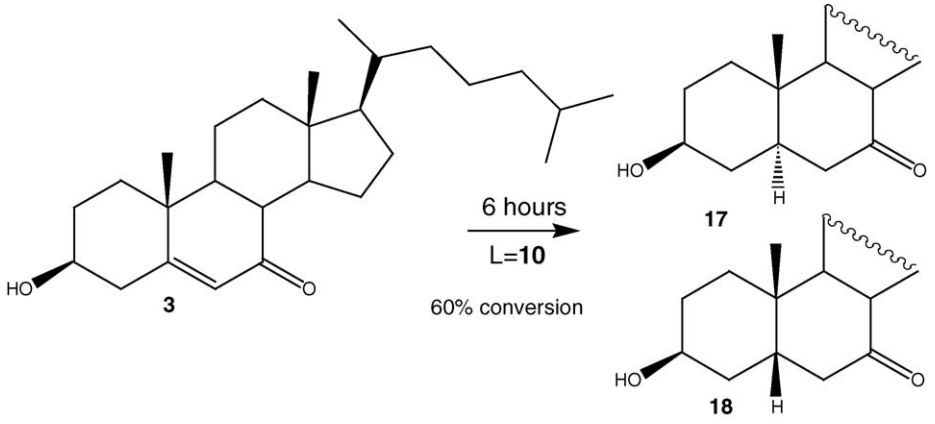
The relative chemoselectivities observed for the hydrogenation of steroid **2** shows that the hydrogenation of Δ^1 double bond is followed by the Δ^4 double bond reduction at different rates, but none of the catalytic systems studied allowed a selective Δ^1 reduction. However, the overall results emphasize that a regioselective reduction of the Δ^1 or Δ^4 can be achieved by the appropriate design of ligand structure and homogeneous catalytic reaction conditions.

The highest diastereoselectivity in the reduction of dienone **2** was achieved for reactions performed in the absence of phosphorous ligands (Table 2, entry 1) as well as in the presence of the bulky phosphite **6** (Table 2, entry 3). Due to the simultaneous presence of Δ^1 and Δ^4 double bonds, ring A is slightly bent out of the plane of ring B. Therefore, since both faces of steroid **2** have similar steric hindrance, the diastereoselectivity decreases when the Δ^1 and Δ^4 reduction activities are comparable (Table 2, entries 2 and 6).

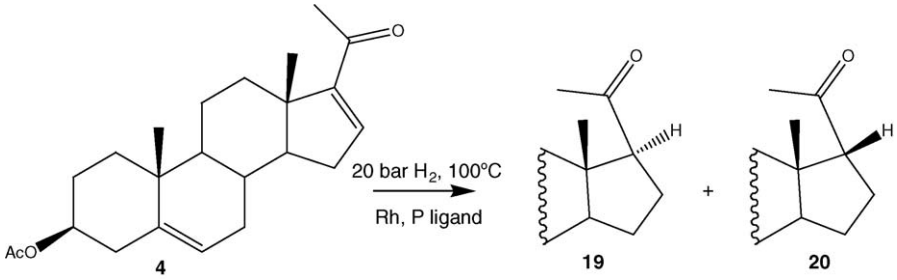
To evaluate the effect of substrate structure on the activity, chemo- and diastereoselectivity of the catalytic homogeneous hydrogenation reactions, these studies were extended to the conjugated enone located at ring B, 3β-hydroxycholest-5-en-7-one **3**, Scheme 4.

In the presence of ligands **5**, **7**, **8** and **9** all the catalytic reductions of steroid **3** gave conversions lower than 10% (3 h). These results are in agreement with previous reports [3,13,14,22,23] that point out the sterical hindrance of steroidal Δ^5 double bonds under different homogeneous catalytic reactions. Again, the highest activity was achieved with ligands **6** and **10**; but only 50% and 60% conversion was obtained, respectively (6 h). After solvent evaporation the crude, without further purification, was analysed by ^{1}H NMR, ^{13}C NMR and GC–MS. The mixture of isomers **17** and **18** was identified as the main products, showing one peak at $\delta = 212.33$ attributed to the saturated C(7) carbonyl group and one signal at $m/z = 402$ (M^+) in the MS-EI.

The study on the activity and selectivity of the homogeneous hydrogenation catalytic processes described above for the endocyclic enones **1**–**3**, was further extended to 3β-acetoxypregna-5,16-dien-20-one **4** containing an exocyclic carbonyl group. Ligand **6**, under the previously mentioned catalytic reaction conditions, allowed a high conversion in a very short reaction time (88% in 5 min), emphasizing the easier approach of the catalytically active species to the less hindered Δ^{16} double bond of substrate **4**. Thus, for comparative purpose, the reduction was performed with a five-fold dilution of the catalyst solution. The results are summarized in Table 3. The main diastereoisomer obtained was isolated and identified by 2D NMR techniques COSY, HSQC and NOESY as being the ketone **19**, Scheme 5.



Scheme 4.



Scheme 5.

The highest conversion was obtained with diphosphite **10** (Table 3, entry 7). All the catalytic systems presented almost complete chemoselectivity for the C=C bond of the exocyclic enone system. In this case, the angular 18-methyl group at C13 together with 17-acyl group led to a very high α-diastereoselectivity (98%) due to the preferred α-side approach of the catalyst.

From the overall results described it is possible to infer that depending on the reaction conditions and ligand structure the Rh(I) monohydride or Rh(III) dihydride can be involved in the catalytic cycle [17]. The different activities obtained with $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ and $[Rh_2(\mu\text{-}Cl)_2(cod)_2]$ precursors (Table 1, entries 1, 3, 6 and 7) and also the significant influence of the addition of Et_3N (Table 1, entry 5) suggest that the bases ^{-}OMe or Et_3N are able to move equilibrium (1) towards the Rh(I) monohydride [14] species which possesses higher activities [17,24–26].

$$[H_2Rh^{III}S_mL_n]^+ + B \rightarrow HRh^{I}S_mL_n + BH \quad (1)$$

Obviously, the acidity of the Rh(III) dihydride depends on the type and number of ligands coordinated to the metal. The presence of π-acid ligands (phosphite) favours the Rh(I) monohydride species [27,28] while triphenylphosphine and the basic alkyldiphosphines stabilize the Rh(III) dihydride complex.

4. Conclusion

The chemo- and stereoselectivities observed in the hydrogenation of α,β-unsaturated oxosteroids, performed with homogeneous rhodium catalysts depend on substrate structure, solvent, catalytic precursor and ligand. Independently of the ligand used, all the homogeneous catalytic systems prepared from $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ precursor in toluene solutions, presented almost complete chemoselectivity for the C=C bond.

The structural characteristics inherent to the steroidal framework, the β-methyl groups C18 and C19 and the 17-acyl group, lead to a very high α-diastereoselectivity, even in the absence of phosphorous ligands. The preferred α-side approach, typical of homogeneous rhodium catalysts, was always obtained whether the ligands were chiral or not. The best stereoselectivity was obtained by the addition of the bulky ligand **6**.

The catalytic system formed in situ from $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ is more reactive than the chlorine precursor even without any addition of bases. The highest activity for C=C hydrogenation was observed with phosphite ligands, being diphosphite **10** the most active. Furthermore, this ligand **10** leads to the formation of a stable catalytic system which reveals a remarkable activity for oxo-group reduction.

Studies on the reduction of carbonyl groups with rhodium homogeneous catalytic systems modified with phosphite ligands are currently underway.

Acknowledgements

The authors thanks FCT, bilateral agreement GRICES-Hungary and CYTED V/9 for financial support.

References

[1] J. Fried, J.A. Edwards, Organic Reactions in Steroid Chemistry, vol. I, Van Nostrand Reinhold Company, New York, 1972, pp. 111–144.
[2] C. Djerassi, Steroid Reactions: An Outline for Organic Chemists, Holden-Day Inc., San Francisco, 1963.
[3] L. Kollár, S. Tôrös, B. Heil, Z. Tuba, J. Mol. Catal. 47 (1988) 33.
[4] G.J.H. Buisman, M.E. Martin, E.J. Vos, A. Kootwijt, P.C.J. Kamer, P.W.N.M. van Leeuwen, Tetrahedron Asymm. 6 (1995) 719.
[5] R. Axet, C. Claver, S. Castillón, in preparation.
[6] M. Aghmiz, A. Aghmiz, Y. Díaz, A. Masdeu-Bultó, C. Claver, S. Castillón, J. Org. Chem. 69 (2004) 7502.
[7] E. Guiu, M. Aghmiz, Y. Díaz, C. Claver, B. Meseguer, C. Militzer, S. Castillón, Eur. J. Org. Chem., in press.
[8] G.J.H. Buisman, P.C.J. Kamer, P.W.N.M. van Leeuwen, Tetrahedron Asymm. 4 (1993) 1625.
[9] P.W.N.M. van Leeuwen, C.F. Roobeek, J. Organomet. Chem. 258 (1983) 343.
[10] R. Uson, L.A. Oro, J.A. Cabeza, Inorg. Synth. 23 (1985) 126.
[11] H. Burrows, M.M. Pereira (Eds.), Síntese e Estrutura, Escolar Editora, Lisboa, 2005.
[12] Dictionary of Organic Compounds, vol. 1, Eyre and Spottiswoode Publishers, London, 1936, pp. 232–233.
[13] Dictionary of Organic Compounds, vol. 1, Eyre and Spottiswoode Publishers Ltd., London, 1953.
[14] S. Tórös, L. Kollár, B. Heil, L. Markó, J. Organomet. Chem. 255 (1983) 377.
[15] S. Deerenberg, O. Pàmies, M. Diéguez, C. Claver, P.C.J. Kramer, P.W.N.M. van Leeuwen, J. Org. Chem. 66 (2001) 7626.
[16] O. Pàmies, M. Diéguez, G. Net, A. Ruiz, C. Claver, J. Org. Chem. 66 (2001) 8364.
[17] R.S. Dickson, Homogeneous Catalysis with Compounds of Rhodium and Iridium, D. Reidel Publishing Company, Dordrecht, 1985, pp. 43–44.
[18] W. Voelter, C. Djerassi, Chem. Ber. Recueil 101 (1968) 58.
[19] C. Djerassi, J. Gutzwiller, J. Am. Chem. Soc. 88 (1966) 4537.
[20] A.J. Birch, J. Chem. Soc. (C) (1966) 1894.
[21] R. Skoda-Földes, L. Kollár, Chem. Rev. 103 (2003) 4095.

[22] A. Wilds, C. Djerassi, J. Am. Chem. Soc. 68 (1946) 1712.
[23] A. Ryer, W. Gebert, N. Murril, J. Am. Chem. Soc. 72 (1950) 4247.
[24] D.L. Dubois, D.W. Meek, Inorg. Chim. Acta 19 (1976) L29.
[25] J. Niewahner, D.W. Meek, Adv. Chem. Ser. 196 (1982) 257.
[26] J. Niewahner, D.W. Meek, Inorg. Chim. Acta 64 (1982) L123.
[27] R.H. Crabtree, The Organometallic Chemistry of the Transition Metals, John Wiley & Sons, New York, 1988.
[28] P.W.N.M. van Leeuwen, Homogeneous Catalysis—Understanding the Art, Kluwer Academic Publishers, Dordrecht, 2004, pp. 11, 75–77.