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Asymmetric Hydrogenation of 3,4-Hexanedione over PtSn Catalysts

Virginia Vetere · María B. Faraoni · Julio C. Podestá · Mónica L. Casella

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Abstract In this work, some results of the liquid-phase racemic and enantioselective hydrogenation of 3,4-hexanedione are presented. The catalysts employed were platinum-based, supported on SiO_2. Monometallic catalysts were modified with organotin precursors either chiral (hexa(−)-menthylditin, $Men_3Sn–SnMen_3$) or achiral (tetrabutyltin, $SnBu_4$), and they were obtained via surface organometallic chemistry on metals techniques. Asymmetric system was selective to 4-hydroxyhexan-3-one, the enantiomeric excess achieved being 17%.

Keywords 3,4-Hexanedione · Asymmetric hydrogenation · PtSn

1 Introduction

The hydrogenation of α-diketones presents an interesting challenge in terms of regio- and enantioselectivity as these compounds have two carbonyl groups susceptible to be hydrogenated. Due to the presence of these two conjugated keto groups, the reaction proceeds in two consecutive steps, the hydrogenation of one of the C=O groups takes place in the first step and the other at a later one [1]. The products of hydrogenation of vicinal ketones, optically active diols and hydroxyketones, are widely used in the pharmaceutical synthesis. An interesting example is 1-phenyl-1,2-propanedione, whose hydrogenation product (R)-1-hydroxy-1-phenyl-2-propanone is an important intermediate in the production of ephedrine derivatives [2].

Most reported work on the heterogeneous enantioselective hydrogenation of carbonyl compounds deals with the use of Pt catalysts modified with alkaloids of the cinchona family [3]. As is well known, these systems are particularly effective in the hydrogenation of α-ketoesters, which yield the corresponding α-hydroxyesters with enantiomeric excesses of up to 98% [4]. To a lesser extent, these systems have been used in the hydrogenation of α-diketones such as 2,3-butanedione, 2,3-hexanedione, 3,4-hexanedione, 1,2-cyclohexanedione and 1-phenyl-1,2-propanedione, reaching enantiomeric excesses generally much lower than those obtained for α-keto esters [1, 5–8].

The reaction products of the hydrogenation of a relatively simple α-diketone, 3,4-hexanedione, are outlined in Fig. 1. As can be seen, in a first stage, two α-hydroxyketones are formed, (4S)- and (4R)-hydroxyhexan-3-one, and in a second step three 3,4-diols, (3S, 4S)- and (3R, 4R)-hexanediol and meso hexanediol are generated. According to data reported in the literature for the hydrogenation of 3,4-hexanedione using Pt/cinchonidine catalysts, the main product obtained is 4-hydroxy-3-hexanone, and the highest enantiomeric excesses reported are ca. 20% in favor of the (R) hydroxyketone [1, 9].

The aim of this work is to study the racemic and enantioselective liquid-phase hydrogenation of 3,4-hexanedione. To achieve this, Pt catalysts modified with organotin compounds, either chiral (hexa(−)-menthylditin, $Men_3Sn–SnMen_3$) or achiral (tetrabutyltin, $SnBu_4$), have been employed. The organobimetallic catalysts were prepared by controlled surface reactions, using techniques derived from surface organometallic chemistry on metals (SOMC/M) [10]. These systems have been successfully

V. Vetere · M. L. Casella (✉)
CINDECA (CCT-La Plata, CONICET, UNLP), 47 no 257, 1900 La Plata, Argentina
e-mail: casella@quimica.unlp.edu.ar

M. B. Faraoni · J. C. Podestá
INQUISUR (CCT-Bahía Blanca, CONICET, UNS) (Miembro de la CIC), Av. Alem N. 1253, 8000 Bahía Blanca, Argentina

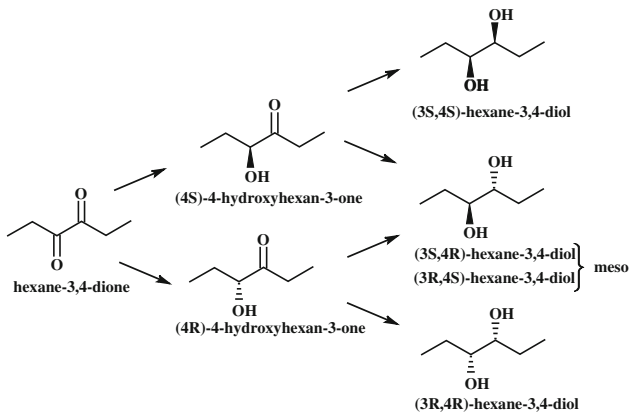

Fig. 1 Reaction pathway for 3,4-hexanedione hydrogenation

used by our research group in the enantioselective hydrogenation of other prochiral carbonyl compounds [11, 12].

2 Experimental Section

2.1 Synthesis and Characterization of Hexa(−)-Menthylditin ($Men_3Sn–SnMen_3$)

The reaction was carried out following the Podestá and Radivoy technique [13]. A volume of 150 mL of a 1.58 M (0.240 mol) solution of (−)-menthylmagnesium chloride in dry THF was added drop by drop to a solution of 10.3 g (0.040 mol) of $SnCl_4$ in 48 mL of dry C_6H_6, in an ice bath. Once the addition step was finished, the reaction mixture was heated under reflux for 60 h and then it was cooled down to room temperature under stirring. A 10% HCl solution (25 mL) was added and diluted with distilled water (25 mL). After the addition of ethyl ether (200 mL), the organic phase was separated and dried on anhydrous $MgSO_4$. The solvent was distilled under reduced pressure, and the product was recrystallized in ethanol, yielding 12.9 g (0.012 mol, 59.8%) of hexa(−)-menthylditin ($Men_3Sn–SnMen_3$; Men: menthyl); m.p. 503 K (dec.), $[\alpha]_D^{20} = -214$ (0.99; dry benzene). The obtained compound was characterized by NMR of ^1H, ^{13}C and ^{119}Sn in a Bruker ARX 300 apparatus, using $CDCl_3$ with tetramethylsilane as the standard.

2.2 Catalysts Preparation

The monometallic catalyst was prepared by ion exchange, using SiO_2 as support (Aerosil Degussa, 180 $m^2\ g^{-1}$), previously treated with ammonia solution. The solid, properly functionalized, was contacted with an aqueous solution of $[Pt(NH_3)_4]Cl_2$ in an appropriate concentration so as to obtain 1 wt% Pt in the resulting catalyst. After 24 h of exchange at room temperature, the solid was separated by filtration, washed and dried at 378 K, and subsequently reduced in H_2 flow at 773 K for 2 h.

The modification of monometallic catalysts by tin addition was carried out by using SOMC/M techniques [10 and references cited therein]. Based on the deep analysis of catalytic systems analogous to the ones here presented, the experimental conditions were selected so as to achieved the desired Sn/Pt atomic ratio [14–16]. After the reduction stage, a definite quantity of the monometallic catalyst (0.25 g) was put to react in H_2 atmosphere with $SnBu_4$ dissolved in *n*-heptane at 363 K. Once the reaction was complete, the catalyst was washed with several portions of *n*-heptane in Ar atmosphere. This catalyst, which has a molar ratio Sn/Pt = 0.4, is denominated Pt–$SnBu_4$ and corresponds to a solid containing butyl groups anchored on the metallic surface. The preparation of the chiral organometallic catalyst was performed by following an analogous procedure, but using a solution of the chiral organotin compound hexa(−)-menthylditin in *n*-heptane. The Sn/Pt ratio used was also 0.4. This catalyst is denominated Pt–Sn_2Men_6.

2.3 Catalysts Characterization

The monometallic catalyst was characterized by atomic absorption spectrometry (Varian Spectra AA55), temperature-programmed reduction (TPR) (Quantachrome, 25 $cm^3\ min^{-1}$, 5% H_2 in N_2, 10 K min^{-1}), and H_2 and CO chemisorption with a catalyst characterization equipment RXM-100 (Advanced Scientific Designs Inc., USA). The specific surface area of the support was also measured (Micromeritics ASAP 2020, N_2 adsorption at 77 K).

The content of Sn fixed in each organobimetallic catalyst was obtained by chromatographic analysis of the solution containing the organometallic compound, as a function of reaction time, using a Varian CP-3800 gas chromatograph, equipped with a capillary column Factor-Four CP8907 (VF-1 ms, 15 m 0.25 mm i.d., DF = 0.25) and a FID detector. These results were consistent with the values obtained from the analysis of the metal content of bimetallic PtSn catalysts carried out by atomic absorption spectrometry [14]. Measurements of the metal contents after the catalysts have been used in the hydrogenation reaction showed no variation, indicating that there is no metal leaching.

The metal particle size distribution of all catalysts used was measured by transmission electron microscopy (TEM), in a JEOL 100 Cx microscope.

2.4 Hydrogenation Reactions

Both the racemic and the enantioselective hydrogenations of 3,4-hexanedione were carried out in a stirred autoclave-type reactor at a H_2 pressure of 1 MPa and a temperature of

353 K, using 0.25 g catalyst, and 2-propanol as solvent. In each test, 0.4 mL of 3,4-hexanedione and 60 mL of 2-propanol were used (0.06 M). The experimental conditions for the catalytic tests were chosen so that the reaction rate was not influenced by mass transfer. Reaction rates were measured at short reaction times and conversion values below 10%. The course of the reaction was followed in a Varian CP-3800 gas chromatograph equipped with a capillary column CP wax 52 CB (30 m, i.d. 0.53 mm) and a FID detector. The reaction products were identified using a GC/MS Shimadzu QP5050 with a capillary column SUPELCO SPB^{TM}-5 (30 m, i.d. 0.25 mm). The enantiomeric excess (ee) was calculated according to the following expression: $ee\% = 100(S - R)/(S + R)$, taking into account data obtained with a BETA DEX^{TM} 120 capillary column (30 m length and i.d. 0.25 mm) in a Varian CP-3800 gas chromatograph.

3 Results and Discussion

3.1 Synthesis and Characterization of Hexa(−)-Menthylditin ($Men_3Sn–SnMen_3$)

A key step in the preparation of the enantioselective heterogeneous catalyst employed in this work is the synthesis of the organotin precursor used as chiral modifier.

The first systematic study of the synthesis of chiral organotin compounds was conducted by Gielen and coworkers [17, 18]. Due to the configurational instability of the most common intermediates in the synthesis of chiral organotin compounds, triorganotin halides, many techniques have been developed to try to stabilize the configuration of these compounds [19, 20]. In order to control the configuration of the metal, Schumann et al. [21] anchored a (−)-menthyl ligand to a tin atom. In 1994 Podestá and Radivoy [13] obtained the hexa-(−)-menthylditin from which other (−)-menthyl derivatives can be synthesized. Their studies confirmed that by binding the (−)-menthyl ligand to a tin atom through the reaction of (−)-menthylmagnesium chloride and tin tetrachloride, the configuration is retained. Different routes have been reported to synthesize chiral organotin compounds, either with a chiral carbon atom directly bonded to the tin atom or the chiral center being far away from it [22]. Due to the fact that chiral organotin compounds containing the chiral carbon atom directly attached to Sn exercise a higher asymmetric induction than those where the chiral center is more remote, it was interesting to synthesize (−)-menthyltin derivatives for using them in the preparation of chiral heterogeneous catalysts [23]. The (−)-menthyl radical has three chiral centers with the configuration (1R, 2S, 5R). In the organometallic compound synthesized in this work, the

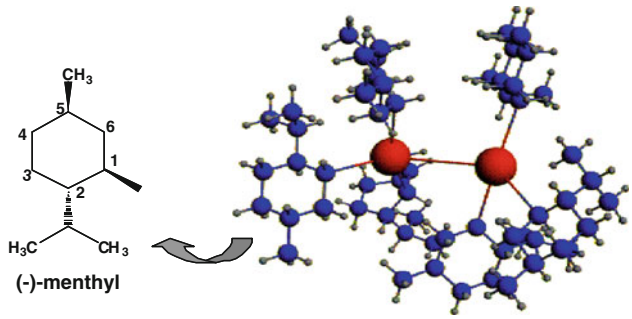

Fig. 2 Structure of hexa-(−)-menthylditin. H (*grey circle*); C (*blue circle*); Sn (*red circle*)

C1 carbon atom of the (−)-menthyl group is the one attached to the Sn atom. However, it is supposed that the enantioselectivity is not only given by the chiral center directly attached to Sn, but also by a steric effect caused by the (−)-menthyl group as a whole. The structure of the (−)-menthyl group and of the chiral organotin precursor compound, (−)-$Men_3Sn–Sn(-)Men_3$ are depicted in Fig. 2.

The (−)-hexamenthylditin was obtained by direct alkylation of tin tetrachloride ($SnCl_4$) and (−)-menthylmagnesium chloride [(−)-MenMgCl]. The following equation outlines the reaction involved in this synthesis:

$$(-)\text{-MenMgCl} + SnCl_4 \xrightarrow{\text{THF/benzene}} (-)\text{-}Men_3Sn-Sn(-)Men_3$$

Besides hexa(−)-menthylditin, tri(−)-menthyltin chloride [(−)-Men_3SnCl] and di(−)-menthyltin dichloride [(−)-Men_2SnCl_2] are also obtained. Studies carried out on the variation of the experimental parameters in the reaction yield allowed optimizing the conditions in order to obtain the highest proportion of the desired product [24].

The ^{1}H, ^{13}C and ^{119}Sn NMR characteristics of the synthesized compound are:

- ^{1}H NMR[1]: 0.73 (d, 18H); 0.79 (d, 18H); 0.84 (d, 18H); 1.07–2.17 (m, 60H).
- ^{13}C NMR[2]: 17.32; 22.10; 22.42; 27.63 (46,3); 34.43 (11,8); 35.70; 36.54 (63,7); 39.62 (196,4); 45.50; 46.30 (19,0).
- ^{119}Sn NMR[3]: 18 ppm.

These results indicate that the compound was obtained optically pure, without epimerization in the carbon atom of the menthyl group bonded to the tin atom.

[1] In $CDCl_3$; chemical shifts, δ, in ppm with respect to TMS; multiplicity, n°H, coupling constants nJ(Sn,H) in Hz, in parenthesis.

[2] In $CDCl_3$; chemical shifts, δ, in ppm with respect to TMS; coupling constants ^{n}J(Sn,C) in Hz, in parentheses.

[3] In $CDCl_3$; chemical shifts, δ, in ppm with respect to $(CH_3)_4Sn$.

3.2 Preparation and Characterization of the Catalysts

The preparation of the base Pt/SiO_2 catalyst (1 wt% Pt, measured by atomic absorption spectrometry) was achieved by means of ionic exchange, a procedure that allowed obtaining a catalytic phase with high dispersion (H/Pt = 0.65 and 0.55, measured by H_2 and CO chemisorption, respectively) [25, 26]. Results obtained by TEM showed a rather uniform distribution of metallic particle size, centered around 2.5 nm. These characteristics of surface homogeneity and dispersion are essential to assure a correct preparation of organometallic catalysts through SOMC/M techniques.

Tin-modified catalysts were obtained by a controlled surface reaction between the monometallic catalyst, previously reduced, and a solution of the organometallic tin compound in a paraffinic solvent, such as *n*-heptane. The reaction takes place between 363 and 423 K and results in a system with organotin moieties anchored to the surface. The following equation represents the above-mentioned process:

$$Pt/SiO_2 + ySnR_4 + \frac{xy}{2}H_2 \rightarrow Pt(SnR_{4-x})_y/SiO_2 + xyRH$$

R represents the remaining organic fragment bonded to tin, that is, butyl or (−)-menthyl group. The amount of tin fixed was measured to determine the "*y*" value (y = Sn/Pt = 0.4). In order to study the specificity of the interaction between the monometallic catalyst and the organotin compounds, blank experiments were conducted in which the tin precursor was contacted with SiO_2. No detectable amounts of tin on the support were observed under the experimental conditions of this work. Unfortunately, it has not been possible to characterize in detail the chiral catalytic systems, in particular as regards the structure of the organotin phase attached to the platinum surface. However, the results presented below, and other published previously [11, 12], show that these systems induce enantioselectivity in the hydrogenation of certain prochiral carbonyl compounds, concluding that at least some (−)-menthyl groups are anchored on the catalyst.

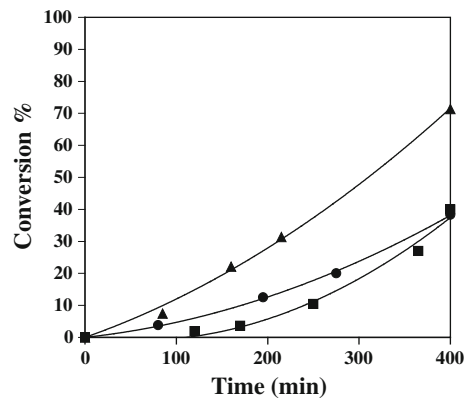

Fig. 3 Hydrogenation of 3,4-hexanedione. Pt (*filled circle*); Pt–$SnBu_4$ (*filled square*); Pt–Sn_2Men_6 (*filled triangle*)

3.3 Catalytic Tests

Figure 3 shows the results of conversion versus time for the hydrogenation of 3,4-hexanedione. As can be seen, in terms of activity, the catalysts behave quite differently. The monometallic catalyst is slightly more active than the $SnBu_4$-modified system, and both are significantly less active than the Pt–Sn_2Men_6 chiral catalyst. To explain these facts it is necessary to take into account the variations in the characteristics of the active sites for hydrogenation that could appear by the addition of either a nonchiral ($SnBu_4$) or a chiral (Sn_2Men_6) organotin modifier. Pt-based catalytic systems modified with $SnBu_4$, similar to those used in this work, have been characterized by our research group using EXAFS, XANES and XPS techniques in order to clarify the nature of the active sites [16, 27]. Those studies revealed that in organobimetallic systems there is a convergence of geometric (dilution of Pt sites) and electronic (increased electron density of Pt) effects due to the presence of Sn. It was also found that Sn is present on the surface of Pt both in ionic form, Sn(II, IV), and in metallic form, Sn(0).

The initial reaction rates for all systems are reported in Table 1. For the racemic hydrogenation of 3,4-hexanedione a certain decrease in the initial reaction rate can be seen when the monometallic catalyst is modified with $SnBu_4$.

Table 1 Initial reaction rate, conversion and selectivity at 400 min

Run	Catalyst	r_i^a	Conversion (%)	S_I (%)[b]	S_{II} (%)[b]	S_{III} (%)[b]	ee_I%[c]	ee_{II}%[c]
1	Pt	14	38	82	6	12	0	0
2	Pt–$SnBu_4$	9	40	31	13	56	0	0
3	Pt–Sn_2Men_6	29	71	56	12	32	17	5

[a] Reaction rate estimated between 0 and 10% conversion. r_i (μmol g_{Pts}^{-1} s^{-1})

[b] I = (4S)- and (4R)-hydroxyhexan-3-one; II = (3S,4S)- and (3R,4R)-hexanediol; III = meso hexanediol

[c] ee% = 100(S − R)/(S + R)

The presence of SnBux fragments blocks some active sites for the hydrogenation on the Pt surface and, as a consequence, the catalytic activity is reduced. The situation is quite different for the chiral systems; Fig. 3 and Table 1 show that there is a significant increase in activity when the monometallic catalyst is modified with the chiral inductor Sn_2Men_6. The presence of (−)-menthyl chiral fragments on the surface might be responsible for some kind of geometric interaction with the substrate, which would cause a rate acceleration in the key step of enantiodifferentiation. This phenomenon has already been reported in previous studies for the hydrogenation of 3,4-dimethoxyacetophenone using the same chiral inductor [11] and goes in the same direction as the commonly observed effect in the enantioselective hydrogenation using classical Pt-cinchonidine systems [3, 28]. The rate-promoting effect of tin on the enantioselective hydrogenation of 3,4-hexanedione over polymer-stabilized platinum nanoclusters has been investigated by Zhang et al. These authors also found that the enantioselectivity could be enhanced by the addition of Sn^{2+}, probably due to the electrophilic nature of Sn^{2+} [29].

Table 1 reports the selectivity to the different products from the hydrogenation of 3,4-hexanedione. As already mentioned, the reaction proceeds in two stages. In a first step the hydrogenation of one of the C=O groups takes place, yielding 4-hydroxyhexan-3-one, and then the hydrogenation of the other C=O group occurs, producing 3,4-hexanediol. As shown in Table 1, when using the monometallic catalyst, 4-hydroxyhexan-3-one is the main product obtained, and to a lesser extent, 3,4-hexanediol. The addition of Sn changes the catalytic behavior in terms of selectivity, significantly increasing the amount of diols obtained. Ionic Sn species on the surface of the base metal act as electrophiles or Lewis acid sites for the adsorption and activation of the C=O group via the free electron pair of the oxygen atom, promoting the attack of the carbonyl group by the chemisorbed hydrogen and favoring the second stage of hydrogenation, i.e., the production of 3,4-hexanediol from 4-hydroxyhexan-3-one.

It is interesting to note that, for none of the catalytic systems used in this work, the formation of a hemiketal between the solvent (2-propanol) and 3,4-hexanedione or 4-hydroxyhexan-3-one has been detected. According to what has been reported in the literature, these by-products have been observed in the hydrogenation of 2,3-butanedione in the presence of ethanol as solvent [1].

The Pt–Sn_2Men_6 system also proved to be enantioselective in both the first and the second hydrogenation steps, the enantiomeric excess reaching values of 17 and 5% for 4-hydroxyhexan-3-one and 3,4-hexanediol, respectively. The enantiomeric excess obtained for the hydroxy ketone is comparable to that reported in the literature when the classical systems Pt/cinchonidine are used [1, 9]. The chiral catalyst proposed in this work has another advantage, which is the possibility of being reused, keeping both its activity and chemo- and enantioselectivity in several successive cycles of hydrogenation, as has been previously reported for the enantioselective hydrogenation of other prochiral carbonyl compounds [12].

4 Conclusions

The main findings of this study are summarized below:

- It has been possible to prepare organobimetallic catalysts by the selective reaction of an organotin compound ($SnBu_4$ and Sn_2Men_6) and a Pt-based catalyst. These systems have been obtained through controlled surface reactions, using techniques derived from SOMC/M.
- These solids proved to be active catalysts in the hydrogenation of 3,4-hexanedione. The achiral Pt–$SnBu_4$ catalyst presented a slightly lower activity than the corresponding monometallic catalyst, possibly due to a dilution effect of the active sites on the Pt surface, due to the presence of Sn.
- For the chiral system Pt–Sn_2Men_6, there was a significant increase in the hydrogenation rate, which could be due to the presence of (−)-menthyl groups on the surface that would cause some specific interaction with the substrate, accelerating the reaction rate in the key step of enantiodifferentiation.
- The Pt–Sn_2Men_6 catalyst proved to be enantioselective in the two steps of the hydrogenation, reaching values of enantiomeric excess of 17 and 5% for 4-hydroxyhexan-3-one and 3,4-hexanediol, respectively. The enantiomeric excess obtained for the hydroxy ketone is comparable to those achieved with classical enantioselective systems.

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