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Enantioselective Hydrogenation of 1-Phenyl-1,2-propanedione

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Enantioselective hydrogenation of a diketone, 1-phenyl-1,2-propanedione was studied in a pressurized reactor at 5 bar and at 0–25°C in different solvents: ethanol, ethyl acetate, and dichloromethane over platinum catalysts. Both *in situ* modification (simultaneous addition of the reagent and the modifier) and premodification (preadsorption of the modifier prior to the reagent) of the catalyst were investigated using cinchonidine as catalyst modifier. Racemic hydrogenation proceeded with nearly the same rate as the selective hydrogenation in the presence of the catalyst modifier. The kinetic results revealed that the hydrogenation of the carbonyl group attached to the phenyl ring was preferred, the main product being 1-hydroxy-1-phenylpropanone; the ratio between 1-hydroxy-1-phenylpropanone and 2-hydroxy-1-phenylpropanone was about 11. The most effective and enantioselective catalyst was obtained by *in situ* modification in dichloromethane yielding in 67 mol% of (*R*)-1-hydroxy-1-phenylpropanone, corresponding to the enantiomeric excess of 64%. The enantiomeric excess was independent of the reactant conversion. In the second hydrogenation step the main product among diols was (1*R*,2*S*)-1-phenyl-1,2-propanediol. © 2001 Elsevier Science

Key Words: **enantioselective hydrogenation; 1-phenyl-1,2-propanedione; cinchonidine; solvent; modification.**

INTRODUCTION

One of the most important requirements for heterogeneous catalytic reactions in fine chemicals production is proper selectivity, which in a broad sense should be understood as chemo-, regio-, and enantioselectivity. Enantioselective reactions in heterogeneous catalysis are of growing interest, as optically pure chiral compounds are of great importance in the areas of pharmaceuticals, agrochemicals, flavors, and fragrances. It is well recognized that different enantiomers can possess different physiological properties, sometimes the "wrong" enantiomer being a ballast, sometimes a "pollutant." Catalytic hydrogenation of ketones with a prochiral center over nonchiral catalysts produces racemic mixtures of optical isomers. Heterogeneous asymmetric catalysis with the participation of modifiers has proven to be an efficient way of producing optically pure chiral substances, as handling and separation is much more simple than applying homogeneous catalysts. The role of the modifier is to steer the adsorption of the reagent in such a way that enantioselective hydrogenation is enabled. Heterogeneous enantioselective hydrogenation of α-ketoesters with a Pt catalyst modified by alkaloids such as cinchonidine has been studied intensively during recent years (1). However, there exist very few publications concerning the enantioselective hydrogenation of conjugated diketones (2–8), where an analogously modified catalyst system could be used. The products, chiral α-hydroxyketones, are valuable building blocks in the asymmetric synthesis of biologically active compounds (9) and they are also intermediates in the synthesis of anti-AIDS drugs (10). Also chiral amino alcohols, which are used as vasoconstriction agents (11), are synthesized from enantiomerically pure hydroxyketones. In the present study, we have chosen 1-phenyl-1,2-propanedione (**A**) as a model compound in enantioselective hydrogenation. The reaction scheme is displayed in Fig. 1.

Two kinds of regioisomeric intermediates, 1-hydroxy-1-phenylpropanone and 2-hydroxy-1-phenylpropanone, may exist in the system. The reaction proceeds further to 1-phenyl-1,2-propanediols. The aim of this work was to investigate the enantioselective hydrogenation of 1-phenyl-1,2-propanedione and to maximize the selectivity of the formation of (*R*)-1-hydroxy-1-phenylpropanone, which was the most prominent product. The catalysts were Pt/Al_2O_3 and Pt/C, modified with cinchonidine.

EXPERIMENTAL

1-Phenyl-1,2-propanedione (Acros, 20736-0050, 98%) was hydrogenated in a pressurized reactor (Sotelem, Microautoclave System, volume 100 cm^3). The stirring rate was 1600 rpm. The hydrogen (AGA, 99.999%) pressure was 5 bar and temperature was 0–25°C. Two different Pt catalysts were used: Pt/Al_2O_3 (Strem Chemicals,

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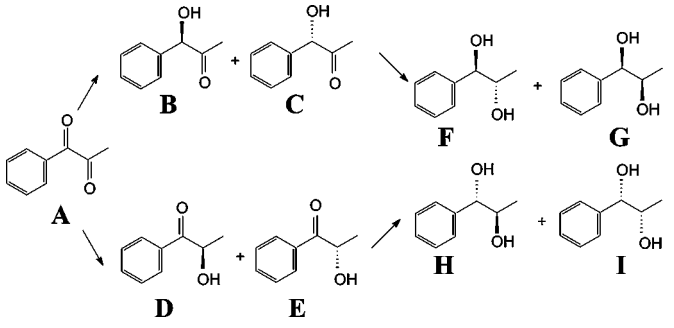

FIG. 1. Reaction scheme in the hydrogenation of 1-phenyl-1,2-propanedione. Symbols: **A**, 1-phenyl-1,2-propanedione; **B**, (*R*)-1-hydroxy-1-phenylpropanone; **C**, (*S*)-1-hydroxy-1-phenylpropanone; **D**, (*R*)-2-hydroxy-1-phenylpropanone; **E**, (*S*)-2-hydroxy-1-phenylpropanone; **F**, (1*R*,2*S*)-1-phenyl-1,2-propanediol; **G**, (1*R*,2*R*)-1-phenyl-1,2-propanediol; **H**, (1*S*,2*R*)-1-phenyl-1,2-propanediol; and **I**, (1*S*,2*S*)-1-phenyl-1,2-propanediol.

78-1660) metal content 5 wt%, BET specific surface area 95 m^2/g, mean metal particle size 8.3 nm (XRD), dispersion 40% (H_2 chemisorption), the mean catalyst particle size 18.2 μm (Malvern), and Pt/C (Alfa 5R18) metal content 5 wt%, BET specific surface area 988 m^2/g, mean metal particle size 1.5 nm (XRD), mean catalyst particle size 15.1 μm (Malvern). The catalysts were activated prior to the reaction under hydrogen flow (100 cm^3/min) for 2 h at 400°C and cooled down to the reaction temperature. Two different catalyst modification procedures were tested:

(1) *In situ* modification: the deoxygenated solution, containing the solvent, the modifier, and the substrate, was injected into the reactor, where the activated catalyst was under hydrogen and the reaction was commenced immediately. The modifier-to-catalyst mass ratio was 1 : 1. Typically the amounts of catalyst, substrate, and modifier were 60, 75, and 60 mg.

(2) Premodification: after cooling the activated catalyst to the reaction temperature, a solution (40 cm^3) containing an excess of the modifier (0.68 mmol) was injected into the reactor and was stirred in the presence of air for 1 h. Then the solvent was removed in such a way that the catalyst remained covered by a thin layer of liquid, and the reactor was flushed with hydrogen. Fresh solvent and the substrate were injected into the reactor and the reaction was started. Typical amounts of catalyst and substrate were 60 and 75 mg, respectively.

The initial concentration of 1-phenyl-1,2-propanedione was 0.01 mol/dm^3 in all experiments. Three different solvents were studied: ethanol (Etax, Primalco, 99.5%,), ethyl acetate (FF Chemicals, 99.8%), and dichloromethane (Merck, 822271, >99%), and 0.04 mol/dm^3 acetic acid in ethanol. The mass ratio of 1-phenyl-1,2-propanedione-to-platinum was 25 in all experiments. The catalyst was modified with (-)-cinchonidine (Aldrich, C8040-7, 96%).

Samples were withdrawn from the reactor at different time intervals and analyzed with a gas chromatograph (GC) (Varian 3300) equipped with a chiral column (β-Dex 225; length 30 m, diameter 0.25 mm, film thickness 0.25 μm). Helium was used as a carrier gas with a split ratio of 33. The detector (FI) and injector temperatures were 270 and 240°C, respectively. The temperature program of the GC was 110°C (30 min)–15°C/min–250°C (31 min). The GC analysis was calibrated with 2-phenyl-1,2-propanediol (Aldrich, 21376-4, 97%) and with racemic 1-hydroxy-1-phenyl-2-propanone (57.9%) and 1-phenyl-2-hydroxy-1-propanone (95.9%, by NMR), which was synthesized at the Laboratory of Polymer Technology, Åbo Akademi (the synthesis part is described in the Appendix). The internal standard in the GC analysis was 1-octanol (Merck, 991, 97%) and the samples were diluted with *n*-hexane (Merck, 4368, 95%). The assignment of the peaks obtained by analyzing the hydrogenation products of 1-phenyl-1,2-propanedione in the GC was carried out by using the products of the asymmetric synthesis of (*R*)-1-hydroxy-1-phenylpropanone (**B**, Fig. 1) and (1*R*,2*S*)-1-phenyl-1,2-propanediol (**F**, Fig. 1) (synthesis procedures are described in the Appendix).

Catalyst Characterization

Mean metal particle size was measured via X-ray diffraction (XRD) carried out using a Phillips PW 1830 X-ray powder diffractometer and PW 1710 diffractometer control. A Cu anode with 2 kW power was used as X-ray source.

Hydrogen chemisorption measurements were performed using an automatic chemisorption apparatus (Sorptomatic 1900, Carlo Erba Instruments). Adsorption isotherms were recorded at 25°C and within the pressure range of 1.3–130 mbar. The catalyst was first reduced at 400°C for 2 h with flowing hydrogen. After the reduction, the catalyst was evacuated at 10^{-4} bar for 1 h at 400°C.

The BET specific surface areas were measured with the automatic physisorption–chemisorption apparatus (Sorptomatic 1900, Carlo Erba apparatus). The catalyst was degassed at 300°C *in vacuo* prior to the surface area measurement by nitrogen adsorption.

The mean particle sizes of the commercial catalysts were measured with a Malvern Zetasizer IIc apparatus. The size measurement is based on the scattering of He–Ne light, which is reflected to a catalyst powder-ethanol suspension. Interference figures of the scattered light are collected by a Fourier lens and are reflected to the detector. The interference figures are processed by the computer unit of the measurement apparatus to the corresponding catalyst particle size distribution on the basis of light intensity variation of the figures.

The elemental analysis of the Pt catalysts were carried out with the electron probe microanalysis (EPMA) technique using a LEO S360 microscope connected to an X-ray image (IMIX) analyzer (Princeton Gamma Tech).

RESULTS AND DISCUSSION

Choice of Catalyst, Catalyst Modification Procedure, and Solvent

One of the most important parameters of a catalyst modified with cinchonidine might be the mean metal particle size and the dispersion of the metal. In the hydrogenation of ethyl pyruvate, over cinchonidine (CD) modified Pt catalysts, relatively large Pt particles with dispersion lower than 50% have yielded the best results (1). At the same time in ethyl pyruvate hydrogenations the catalyst support plays a minor role and good results were obtained over silica, alumina, and active charcoal as well as with some zeolite-supported catalysts (12, 13). For preliminary testing in the hydrogenation of 1-phenyl-1,2-propanedione, two different commercial catalysts, Pt/C and Pt/Al_2O_3, having 5 wt% metal loadings were chosen. Both alumina and active charcoal-supported Pt catalyst have been active and selective in the enantioselective hydrogenation of ethyl pyruvate (12). The mean metal particle sizes for the studied Pt/C and Pt/Al_2O_3 catalyst were 1.5 and 8.3 nm, respectively, according to the XRD measurements. The BET specific surface areas for the former and latter were 988 and 95 m^2/g. The pores in the alumina support were very large, 57% of the pore volume located in the pores between 10 and 100 nm. The best alumina supports in the hydrogenation of α-ketoesters also had large pores (14). However, the pores in the Pt/C catalysts were somewhat smaller, only 35% of the pore volume located in the pores between 10 and 100 nm.

The energy minimized conformations of cinchonidine, (*R*)-1-hydroxy-1-phenylpropanone and (*R*)-2-hydroxy-1-phenylpropanone *in vacuo*, were modeled with the Cache program (15). Our calculations were in good agreement with the literature data (16). According to our calculations, the most stable conformation of the cinchonidine was analogous with the reported Open (3) conformer of the modifier (16), found previously to be the most stable among the other conformers. The Open (3) conformer is considered to be involved in the enantiodifferentiating transition state. The population of this conformer is thought to be the cause of the observed solvent dependence (16) on enantioselective hydrogenation. The longest dimension in cinchonidine is about 1.1 nm. The product molecules, 1-hydroxy-1-phenylpropanone and 2-hydroxy-1-phenylpropanone had their longest interatomic distances 0.71 and 0.77 nm, respectively. The comparison between the catalyst pore sizes and the molecules in the reaction indicated that the Pt/Al_2O_3 catalyst might be more suitable for enantioselective hydrogenation of 1-phenyl-1,2-propanedione due to the larger fraction of large pores more readily available for the bulky modifier and reactant.

The preliminary hydrogenations of 1-phenyl-1,2-propanedione were carried out at 25°C and 5 bar H_2 in dichloromethane or ethanol (Table 1). The catalysts were either premodified in dichloromethane with 0.68 mmol CD as in the work of Griffiths *et al.* (3) or modified *in situ* with CD. The enantiomeric excess (ee) of (*R*)-1-hydroxy-1-phenylpropanone (**B**, Fig. 1) is defined as

$$\text{ee} = \frac{[\mathbf{B}] - [\mathbf{C}]}{[\mathbf{B}] + [\mathbf{C}]} \cdot 100\%.$$

In the experiment with the premodified catalyst (see Experimental) the ee of **B** with the Pt/C catalyst was close to

TABLE 1

Comparison of Pt/C and Pt/Al_2O_3 Catalyst in Enantioselective Hydrogenation of 1-Phenyl-1,2-propanedione at 25°C at 5 Bar H_2

Catalyst	Modification	Solvent	Initial hydrogenation rate (10^{-5} mol/s m^2)	Max. ee (%)
Pt/C	Premodification in CH_2Cl_2 with 0.68 mmol CD	CH_2Cl_2	0.56	0
Pt/Al_2O_3	Premodification in CH_2Cl_2 with 0.68 mmol CD	CH_2Cl_2	0.12	62
Pt/C	*In situ* with 0.20 mmol CD	EtOH and 2 mmol acetic acid	0.40	17
Pt/Al_2O_3	*In situ* with 0.20 mmol CD	EtOH and 2 mmol acetic acid	0.23	33
Pt/Al_2O_3	*In situ* with 0.20 mmol CD	EtOH	0.35	24
Pt/Al_2O_3	*In situ* with 0.20 mmol CD	CH_2Cl_2	0.13	65[a]
Pt/Al_2O_3	Premodification in CH_2Cl_2 with 0.68 mmol CD	CH_2Cl_2	0.12	13[b], 62[c]

[a] Constant.
[b] Conversion of dione 20%.
[c] Conversion of dione 96%.

0, whereas enantiomeric excesses over 60% were obtained with Pt/Al_2O_3 (Table 1). The second set of experiments was carried out in ethanol in the presence of 0.04 M acetic acid, using *in situ* modification of the catalysts with CD. Acetic acid might protonize cinchonidine and thus have a beneficial effect on the ee (17). The hydrogenation rate was higher with the Pt/C catalyst than with Pt/Al_2O_3, but the ee was lower with the former catalyst than with the latter one, i.e., 17 and 33%, respectively (Table 1). There was, however, a beneficial effect of acetic acid addition on the ee in ethanol, the ee being 24% without acetic acid and 33% with acetic acid.

The low enantiomeric excesses obtained over the Pt/C catalyst can be mainly attributed to the smaller mean Pt particle size, 1.5 vs 8.3 nm (XRD). According to literature, the catalysts with larger mean Pt particle size give higher enantioselectivities (18). It is also known that impurities in the catalyst can decrease the ee as well (18). In the Pt/C catalyst, there were more impurities than in Pt/Al_2O_3 according to EPMA analysis. The most prominent impurity in the Pt/C catalyst was sodium; however, direct attribution of catalyst behavior to Na poisoning is too premature and more experimental data are needed to elucidate the influence of sodium on enantioselectivity.

Regioselectivity (rs) to 1-phenyl-1-hydroxypropanone was defined as

$$\mathrm{rs} = \frac{[\mathbf{B}] + [\mathbf{C}]}{[\mathbf{D}] + [\mathbf{E}]} \cdot 100\%,$$

where **B**, **C**, **D**, and **E** correspond to hydroxyketones, as defined in Fig. 1. The regioselectivities obtained with the Pt/C and Pt/Al_2O_3 catalysts were about the same, the corresponding values being 13 and 11, respectively. Obtained results indicated that the large, 10-fold differences in BET specific surface area of the catalysts had a minor effect on the regioselectivity. For both of the catalysts, the pores were sufficiently large (for Pt/C and Pt/Al_2O_3 catalysts 36 and 57% of the pore volume located in the pores between 10 and 100 nm, respectively) to allow the reactant to adsorb in a suitable mode to induce a high regioselectivity. In the hydrogenation of 1-phenyl-1,2-propanedione over Pt-modified MCM-41 catalysts (having well-defined pores between 2.3 and 4.1 nm), the regioselectivity remained very low (rs = 3), both in the presence and in the absence of cinchiondine (19). The explanation for the low regioselectivity was steric factors; i.e., the bulky reactant could not adsorb in an optimal mode in the narrow pores of MCM-41 and thus lower regioselectivities were obtained. However, this was not the case with studied Pt/C and Pt/Al_2O_3 catalysts, which had sufficiently large pores.

The catalyst modification procedure can have an effect on the enantioselectivity. In order to investigate the catalyst modification procedure, the following experiments were carried out: the modification was carried out in the presence of air with an excess of cinchonidine and the catalyst was modified *in situ* in two different solvents: dichloromethane (Table 1) and ethanol (Figs. 2a, 2b). The hydrogenation rates were lower with the catalyst premodified in the presence of air than with the catalyst modified *in situ*. The ee of **B** was also lower with the premodified catalyst than with the catalyst modified *in situ*. The ee of **B** increased with increasing conversion of dione, when using a premodified catalyst, while it was constant with the catalyst modified *in situ* with CD in dichloromethane as solvent. In ethanol the ee was constant up to 95% conversion of dione, after which it increased due to the kinetic resolution (see Qualitative Kinetics below). According to the literature (2, 3), air could have a beneficial effect on the enantioselectivity, particularly in ethanol. An explanation to our results, i.e., low ee

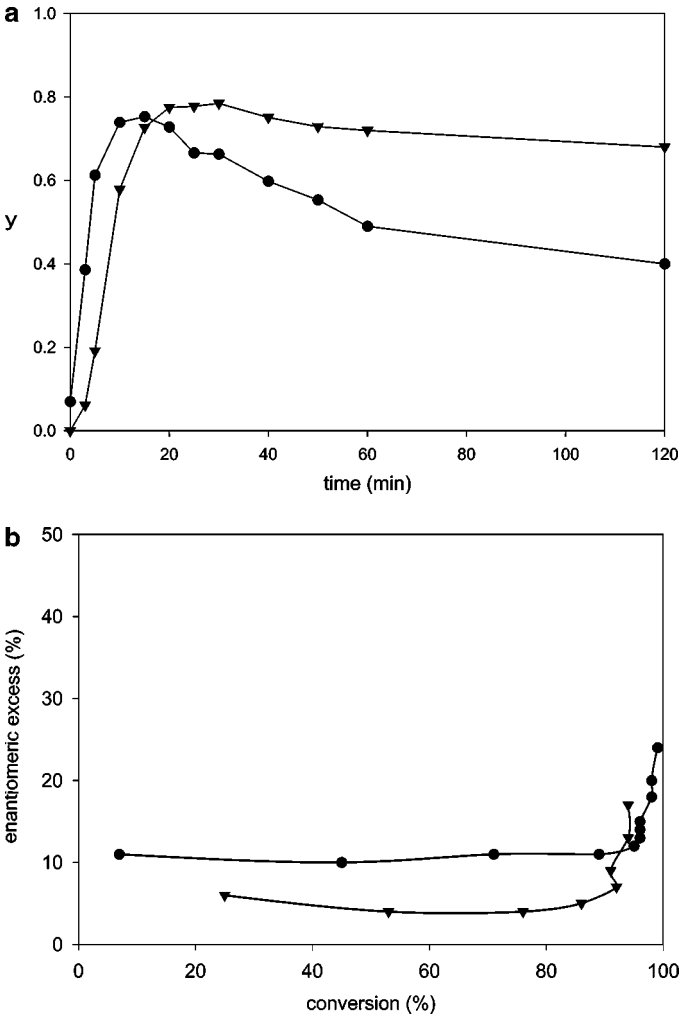

FIG. 2. (a) The yield of 1-hydroxy-1-phenylpropanone in the hydrogenation of 1-phenyl-1,2-propanedione at 25°C in ethanol. The catalyst was modified *in situ* (●) or premodified in the presence of air with an excess of (-)-cinchonidine (▼). (b) The enantiomeric excess of (*R*)-1-hydroxy-1-phenylpropanone in the hydrogenation of 1-phenyl-1,2-propanedione in ethanol at 25°C. The catalyst was modified *in situ* (●) or premodified in the presence of air with excess of (-)-cinchonidine (▼).

in the reaction, could be a partial deactivation of the catalyst in the presence of air and also the excess of cinchonidine, 0.68 mmol in 40 cm^3 during premodification; the amount of cinchonidine was in fact not optimized. In these experiments the solvents included small amounts of dissolved oxygen also in cases, when the catalyst was modified *in situ* and relatively high enantiomeric excesses were obtained. In a previous communication (7), we reported enantioselective hydrogenation of 1-phenyl-1,2-propanedione with solvents distilled under argon. These results indicated that traces of oxygen have a beneficial effect on ee.

When 1-phenyl-1,2-propanedione (the initial concentration 0.01 mol/dm^3) was hydrogenated in the presence of cinchonidine and in the absence of cinchonidine in ethanol at 25°C, the initial hydrogenation rates were nearly the same; i.e., in the absence of cinchonidine the hydrogenation rate was 0.36×10^{-5} mol/s m^2 and in the presence of cinchonidine 0.356×10^{-5} mol/s m^2. In the case of butane-2,3-dione Slipszenko *et al.* (4) have reported a fourfold rate enhancement in the presence of a modifier. In our previous publication with higher initial reactant concentrations (0.05 mol/dm^3) (6), the hydrogenation rate increased and the racemic hydrogenation was faster than the hydrogenation in the presence of cinchonidine, i.e., 1.03 and 0.34×10^{-5} mol/s m^2, respectively. Due to the higher reaction rate the racemic hydrogenation was very unselective; i.e., cyclohexyl products were formed according to GC-MS. From these results we can conclude that the hydrogenation rate increased with increasing initial reactant concentration. There was no rate enhancement compared to the racemic hydrogenation at low initial reactant concentration, whereas at higher initial reactant concentrations in the racemic hydrogenation the unselective hydrogenation became more favorable. The amount of cinchonidine was investigated at 25°C in ethanol; two different cinchonidine-to-catalyst mass ratios were used, 1 : 1 and 1 : 10 (Table 2).

TABLE 2

The Initial Hydrogenation Rate of 1-Phenyl-1,2-propanedione and the Enantiomeric Excess (ee) of (*R*)-1-Hydroxy-1-phenylpropanone over Pt/Al_2O_3 Catalyst at 5 Bar H_2

Solvent	*T* (°C)	Initial hydrogenation rate (10^{-5} mol/s m^2),	Max. ee (%)	Modification
EtOH	25	0.13	13	Premodification in CH_2Cl_2 with 0.68 mmol CD
EtOH	0	0.19	13	*In situ* with 0.20 mmol CD
EtOH	25	0.22	17	Premodification in EtOH with 0.68 mmol CD
EtOH	0	0.22	17	*In situ* with 0.68 mmol CD
EtOH	25	0.32	20	*In situ* with 0.02 mmol CD
EtOH	25	0.36	24	*In situ* with 0.20 mmol CD
CH_2Cl_2	0	0.10	67	*In situ* with 0.20 mmol CD
CH_2Cl_2	15	0.12	63	*In situ* with 0.20 mmol CD
CH_2Cl_2	25	0.13	65	*In situ* with 0.20 mmol CD

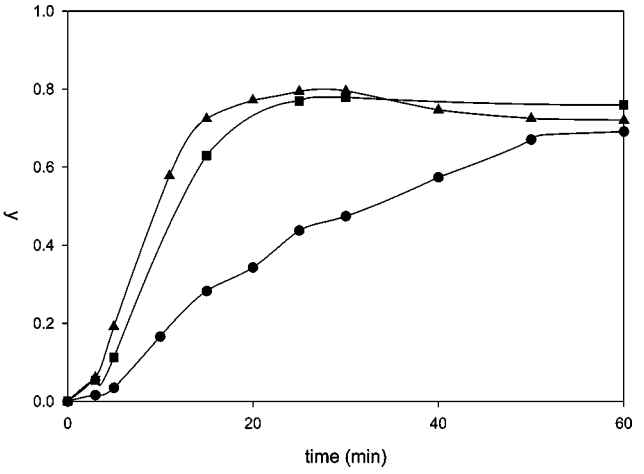

FIG. 3. The yield of 1-hydroxy-1-phenylpropanone in the hydrogenation of 1-phenyl-1,2-propanedione in different solvents at 25°C. The catalyst was premodified in dichloromethane with an excess of (-)-cinchonidine in the presence of air. Symbols: (▲) ethanol, (■) dichloromethane, and (●) ethyl acetate.

The initial hydrogenation rate and the ee increased with increasing modifier concentration from 0.32 to 0.36×10^{-5} mol/s m^2 and from 20 to 24%, respectively. Here we should point out that these results were not yet optimized with respect to the amount of modifier, which will be done for this particular reaction in the future.

1-Phenyl-1,2-propanedione was hydrogenated in three different solvents: ethanol, dichloromethane, and ethyl acetate (Fig. 3). In these experiments, the catalyst was modified with an excess of cinchonidine in the presence of air (see Experimental). The hydrogenation rates increased in the following order: ethyl acetate < dichloromethane < ethanol. The hydrogen solubility increases in the following order: ethanol = dichloromethane (approximated from the solubility of trichloromethane at 25°C: $x_g = 0.000220(20)$) < ethyl acetate (Table 3). The enantiomeric excesses increased with increasing hydrogenation rates in ethanol, whereas in dichloromethane the ee was constant with different initial hydrogenation rates (Table 2). One explanation to this difference in the ee as a function of initial reaction rate in ethanol and in dichloromethane can be that dichloromethane is a rather inert solvent with respect to the Pt surface (4), which increases the possibility of enantioselective hydrogenation. Ethanol is known to be reactive with the Pt surface (22). When comparing different solvents, the highest enantiomeric excesses were obtained with the solvents having the lowest dielectric constants (Table 1). According to literature (23), the highest enantiomeric excesses are obtained with solvents, which have dielectric constants between 2 and 10. It was put forward in (16) that dependence of ee on solvent polarity can be explained by concentration of cinchonidine Open(3) conformers. The population of this conformer from density functional

TABLE 3

The Initial Hydrogenation Rate of 1-Phenyl-1,2-propanedione and the Enantiomeric Excess (ee) of (*R*)-1-Hydroxy-1-phenylpropanone in Different Solvents at 25°C

Solvent	Initial hydrogenation rate (mol/s m^2), 10^{-5}	ee (%)	x_g, 10^{-4}	ε
Ethyl acetate	0.04	13[a], 43[b]	3.43 (20)	6.0 (21)
CH_2Cl_2	0.12	14[c], 62[d]	—	8.9 (21)
EtOH	0.13	10[e]	2.06 (20)	24.6 (21)

[a] Conversion of dione 23%.
[b] Conversion of dione 92%.
[c] Conversion of dione 20%.
[d] Conversion of dione 95%.
[e] Constant.

Note. Catalyst was premodified in dichloromethane with 0.68 mmol CD in the presence of air. Hydrogen solubility (x_g) in different solvents at 25°C and the dielectric constant (ε) of the solvent at 25°C are reported here.

calculations (16) follows the same trend as enantioselectivity with increases of the dielectric constant; i.e., it decreases.

From these preliminary experiments we have chosen one polar and one nonpolar solvent for further testing in enantioselective hydrogenation of 1-phenyl-1,2-propanedione. The Pt/Al_2O_3 catalyst modified *in situ* with cinchonidine resulted in initial reaction rates and enantiomeric excesses higher than those of the Pt/C catalysts and was therefore used in the further testing.

Note that cinchonidine was also hydrogenated in the reaction mixture to dihydrocinchonidine, which was confirmed by GC-MS. We expected to observe the initial transient increase of ee at the beginning of the reaction due to both the hydrogenation of the ethylene group in cinchonidine (two adsorption possibilities for the modifier) and the reaching of the adsorption equilibrium for cinchonidine, similar to what Mallat *et al.* (24) observed in hydrogenation of α-ketoesters. However, in our results the initial development of the ee was not visible; i.e., the observed ee's were already from the beginning at steady state values (Fig. 2b). This can be explained by the excess of cinchonidine in the hydrogenation.

Qualitative Kinetics

The influence of external diffusion was determined by following the published procedure (25), which was previously applied to liquid-phase hydrogenation reactions. Due to rather high values of the reactants' diffusion coefficient, the small particle size of the catalyst, and vigorous stirring (and thus the high value of the specific mixing power) the effect of external diffusion on the reaction rate was negligible. The influence of internal diffusion for porous materials was estimated via calculation of the effectiveness factor η_e for pseudo-first-order reactions with respect to hydrogen, which is related to Thiele modulus ϕ

$$\eta_e = \frac{3}{\phi}\left[\frac{1}{\tanh\phi} - \frac{1}{\phi}\right], \qquad [1]$$

where

$$\phi = \left(k'\rho_p / D_{e_{H_2}}\right)^{1/2} R_p, \qquad [2]$$

where R_p and ρ denote the particle radius and density, and k' is the rate constant for spherical particles. Effective diffusion coefficient $D_{e_{H_2}}$ is obtained from the particle porosity ε_p and tortuosity τ_p, and the Wilke–Chang equation (26) gives

$$\frac{D_{H_2}}{m^2 s^{-1}} = \frac{7.4 \cdot 10^{-12} \cdot \left(\frac{\Phi M}{gmol^{-1}}\right)^{1/2} (T/K)}{\left(\frac{\mu}{cP}\right)\left(\frac{V_{H_2}}{cm^2\ s^{-1}}\right)^{0.6}}, \qquad [3]$$

where Φ is the association factor, M the average molecular mass, and μ the dynamic viscosity.

Apparent hydrogenation rate is given as

$$R' = \eta_e k' c^*_{H_2}. \qquad [4]$$

By combining [1] and [4] one arrives at

$$(a+1)\sinh\phi - \phi\cosh\phi = 0 \qquad [5]$$

with

$$a = \frac{R' R_p^2 \rho_p \tau_p}{3 D_{H_2} \varepsilon_p x^*_{H_2} c_{tot}}, \qquad [6]$$

where $x^*_{H_2}$ is the hydrogen mole fraction in solution.

Results of the calculations (Table 4) showed that the influence of internal mass transfer was practically negligible.

TABLE 4

Evaluation of the Role of Intraparticular Diffusion

T	25°C
P	5 bar
R'	0.0068 mol(kg s)$^{-1}$
R_p	9.1 μm
τ_p	3
ε_p	0.4
ρ_p	1000
c_{tot}	17152
D_{H_2}	0.13021×10^{-8} m^2 s^{-1}
$x^*_{H_2}$	0.0002
ϕ	0.996
η_e	0.94

Note. $c_{tot} = \rho_{mix}/M$.

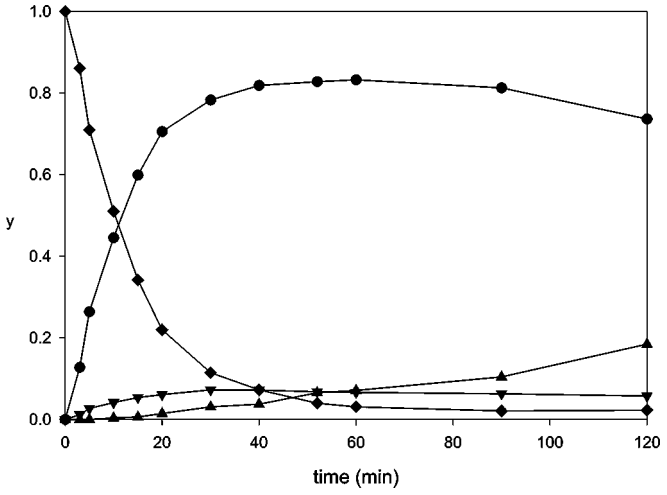

FIG. 4. Hydrogenation kinetics of 1-phenyl-1,2-propanedione in dichloromethane at 25°C. Catalyst: Pt/Al_2O_3 modified *in situ* with (-)-cinchonidine. Symbols: (◆) 1-phenyl-1,2-propanedione, (●) 1-hydroxy-1-phenylpropanone, (▼) 2-hydroxy-1-phenylpropanone, and (▲) 1-phenyl-1,2-propanediol.

Typical hydrogenation kinetics of 1-phenyl-1,2-propanedione is displayed in Fig. 4. In this experiment, 1-phenyl 1,2-propanedione was hydrogenated at 25°C in dichloromethane. The catalyst was Pt/Al_2O_3 modified *in situ* with cinchonidine. The most important product was 1-hydroxy-1-phenylpropanone with the maximum yield of 82%. The ratio between 1-hydroxy-1-phenylpropanone (**B** + **C**, Fig. 1) and 2-hydroxy-1-phenylpropanone (**D** + **E**, Fig. 1) was 11 and that ratio was constant with increasing conversion of dione. Hence the C=O group, which is in the 1-position, can be hydrogenated more readily than the C=O group in the 2-position, close to the methyl group. To answer the question of regioselectivity *ab initio* calculations for 1-phenyl-1,2-propanedione were performed and the details of calculations will be reported in a separate paper (27). It follows from the minimum energy calculations (27) that the carbonyl group and the phenyl ring are coplanar; similar results were reported in (28) for *ab initio* calculations of α-ketoesters with the phenyl ring adjacent to the C=O bond, e.g., ethyl phenylglyoxylate. At the present moment we can only speculate that 1-phenyl-1,2-propanedione is adsorbed preferentially via both the phenyl ring and the C=O bond, thus providing high regioselectivity to 1-hydroxy-1-phenylpropanone.

It is clear from Fig. 4 that diols start to appear in the product mixture right from the very beginning of the reaction. The main product among diols was (1*R*,2*S*)-1-phenyl-1,2-propanediol (**F**, Fig. 1), but not (1*R*,2*R*)-1-phenyl-1,2-propanediol (**G**, Fig. 1). Such a result means *that cinchonidine directs the reaction toward formation of a R-center in the first carbonyl reduction, but toward an S-center in the second carbonyl reduction step.*

Hydrogenation reaction of compounds containing two functional groups can be described involving a "rateau" (rake) scheme (30)

$$\begin{array}{lll} A & & B, C, D, E \\ \Updownarrow & & \Updownarrow \\ A_{ads} \overset{+H_2}{\rightarrow} & (B, C, D, E)_{ads} \overset{+H_2}{\rightarrow} & F, G, H, I. \end{array} \qquad [7]$$

For a similar consecutive reaction $A^{(+H_2)} \rightarrow B^{(+H_2)} \rightarrow F$ it was shown, that it can occur via the mechanism (31, 32)

	$N^{(1)}$	$N^{(2)}$	$N^{(1)'}$	$N^{(2)'}$
$1.A + Z \equiv AZ$	1	0	1	1
$2.AZ + H_2 \rightarrow BZ$	1	0	1	1
$3.BZ + H_2 \rightarrow FZ$	0	1	0	1
$4.BZ \equiv B + Z$	1	−1	1	0
$5.FZ \equiv F + Z$	0	1	0	1

[8]

$N^{(1)}$ $A + H_2 = B$
$N^{(2)}$ $B + H_2 = F$

$N^{(1)'}$ $A + H_2 = B$
$N^{(2)'}$ $A + 2\,H_2 = F.$

Here Z is a site on the surface of the catalyst and AZ, BZ, and FZ are adsorbed species. On the right side of the equations for the elementary steps their stoichiometric numbers along different stoichiometric pathways (routes) are presented. According to the Horiuti–Temkin rule (32, 33) the basic set of pathways in scheme [8] should contain two pathways. Two sets of pathways are shown in the scheme $N^{(1)}$, $N^{(2)}$ and $N^{(1)'}$, $N^{(2)'}$. The final equations of the first set describe the formation of products B and F as sequential, and the second set describes it as parallel. However, if a steady-state or quasi-steady-state reaction is under examination, both descriptions are equivalent in the same way as previously demonstrated for a similar mechanism (30, 31).

Therefore, at least based on present steady-state data, we cannot differentiate between two possible modes of chinconidine influence: direction toward formation of a *R*-center in the first reduction step, but toward an *S*-center in the second during one residence on the surface or via readsorpion of *R*-hydroxyketone. More experiments in a continuous fixed bed reactor under transient conditions as well as quantum chemical calculations are in progress for further elucidation of the reaction mechanism.

The hydrogenation kinetics of 1-phenyl-1,2-propanedione in ethanol were studied at two different temperatures, 0 and 25°C. The catalyst was modified *in situ* in these experiments. The reaction proceeded at highest rate at 25°C (0.356×10^{-5} mol/s m^2), and at that temperature the maximum ee was also slightly higher than that at a lower temperature, about 24% (Table 2). The ee in ethanol was about 12 up to 95% conversion of dione and after that started to increase due to the kinetic resolution, which means

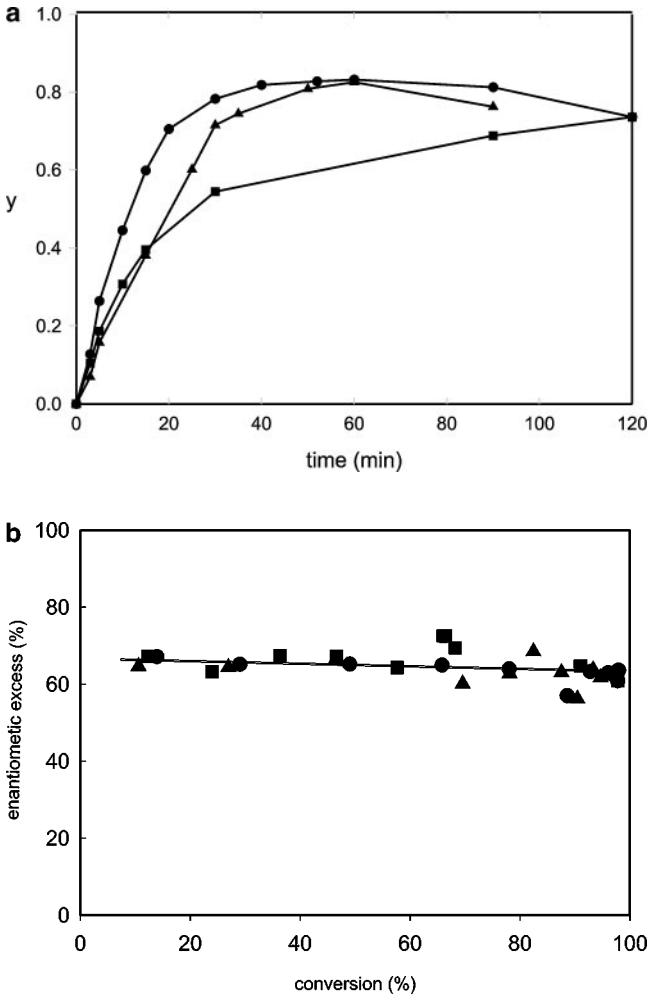

FIG. 5. (a) The yield of 1-hydroxy-1-phenylpropanone in the hydrogenation of 1-phenyl-1,2-propanedione at three temperatures: 0°C (■), 15°C (▲), and 25°C (●) in dichloromethane. Catalyst: Pt/Al_2O_3 modified *in situ* with (-)-cinchonidine. (b) The enantiomeric excess of (*R*)-1-hydroxy-1-phenylpropanone in the hydrogenation of 1-phenyl-1,2-propanedione at three temperatures: 0°C (■), 15°C (▲), and 25°C (●) in dichloromethane. Catalyst: Pt/Al_2O_3 modified *in situ* with (-)-cinchonidine.

that (*S*)-1-hydroxy-1-phenylpropanone reacted faster to diols than its *R*-enantiomer. The effect of temperature in the case of dichloromethane as solvent in the enantioselective hydrogenation of 1-phenyl-1,2-propanedione is shown in Figs. 5a and 5b and in Table 2. The initial hydrogenation rate in dichloromethane was lower than that in ethanol. This difference in the initial hydrogenation rate can be due to the inert dichloromethane; i.e., the catalyst surface is more efficiently modified by cinchonidine in dichloromethane than in ethanol. The ee was about 65%, and it was independent of dione conversion and temperature (Fig. 5b). There was no kinetic resolution observed in dichloromethane as solvent. This could be explained by the fact that the consecutive reaction from hydroxyketones to diols was much slower in the case of dichloromethane; i.e., the yield of diols was 46% in ethanol and 10% in dichloromethane.

CONCLUSIONS

Hydrogenation of 1-phenyl-1,2-propanedione was investigated in a batch reactor at 5 bar and at 0–25°C in different solvents over Pt/C and Pt/Al_2O_3 catalysts. The hydrogenation experiments were carried out under kinetic regime, i.e., in the absence of both external and internal diffusion limitations. In the presence of cinchonidine no rate enhancement was observed; the racemic hydrogenation proceeded with nearly the same rate as the selective hydrogenation in the presence of the catalyst modifier. *In situ* catalyst modification resulted in both a reaction rate and enantioselectivity higher than those in catalyst premodification. The large amount of the modifier and partial catalyst deactivation due to the exposure of air during the premodification were the probable causes for the low enantioselectivity and reaction rate observed over the premodified catalyst. The main product in the first hydrogenation step was 1-hydroxy-1-phenylpropanone; the ratio between 1-hydroxy-1-phenylpropanone and 2-hydroxy-1-phenylpropanone was about 11. Preferentially (*R*)-1-hydroxy-1-phenylpropanone was formed, while in the second hydrogenation step the main product among diols was (1*R*,2*S*)-1-phenyl-1,2-propanediol. Hydrogenation of 1-phenyl-1,2-propanedione over the Pt/Al_2O_3 catalyst showed that it is possible to obtain a high ee (65%) of (*R*)-1-hydroxy-1-phenylpropanone provided that dichloromethane is used as a solvent and the catalyst is preactivated with H_2 and modified *in situ* with cinchonidine. The ee was temperature independent at 0–25°C. The highest enantioselectivities in the hydrogenation of 1-phenyl-1,2-propanedione were obtained for (*R*)-1-hydroxy-1-phenylpropanone with the Pt/Al_2O_3 catalyst with metal particles of 8.3 nm (by XRD). The pores were sufficiently large for the reagents and the modifier to diffuse into them. Contrary to the Pt/Al_2O_3 catalyst, the ee was relatively low over the Pt/C catalyst, which can be attributed to the much smaller metal particle size of the Pt/C catalyst.

In a forthcoming paper optimization of the modifier amount and an investigation of the reaction kinetics will be reported. Further studies to quantify the influence on reaction parameters on regioselectivity and enantioselectivity are in progress.

APPENDIX

Asymmetric Synthesis of (*R*)-1-Hydroxy-1-phenylpropanone

The asymmetric synthesis of (*R*)-1-hydroxy-1-phenylpropanone (**B**, Fig. 1) was performed according to a method

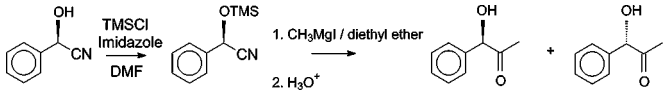

FIG. 6. Reaction scheme in the asymmetric synthesis of (*R*)-1-hydroxy-1-phenylpropanone.

based on the Grignard addition of methylmagnesium iodide to the protected (*R*)-(+)-mandelonitrile ((*R*)-(+)-2-phenyl-2-hydroxyethanenitrile) as depicted in Fig. 6 (33). It is known that the procedure would afford mainly the *R* isomer, since the starting compound for the synthesis was (*R*)-(+)-mandelonitrile.

Protection of the Hydroxyl Group of the (R)-(+)-Mandelonitrile

In a dry round bottom flask, 5.3 g (78 mmol) of imidazole and 75 cm^3 of distilled dimethylformamide (DMF) were added. After cooling to 0°C, 7.2 cm^3 (6.2 g, 57 mmol) of trimethylsilylchloride (TMSCl) was added under stirring. After 15 minutes of stirring, 5.044 g (38 mmol) of (*R*)-(+)-mandelonitrile (Aldrich) was added. The mixture was stirred for 1.45 h at room temperature. The reaction was carried out under argon atmosphere. An amount of 150 cm^3 of water was added and the products were extracted with three 50 cm^3 portions of diethyl ether. The organic layer was dried over sodium sulfate and then the solvent was removed. This procedure afforded a light brown oil. The oil was analyzed by GC (Varian 3300, DB-1 column, 20 m, 0.53 mm i.d.).

Synthesis of the α-Ketol

In a dry round bottom flask, supplied with a reflux condenser and a dropping funnel, under argon atmosphere, 15 cm^3 of a 3 M solution (44 mmol) of methylmagnesium iodide in diethyl ether (Aldrich) and 85 cm^3 of diethyl ether were added. A solution of the oil obtained in the first step in 50 cm^3 of diethyl ether was slowly added through the dropping funnel. The mixture was stirred and refluxed for 6 h. The mixture was added to a flask containing 120 g of ice and 5 cm^3 of concentrated sulfuric acid. The resulting mixture was stirred overnight. The aqueous layer was extracted with three 80 cm^3 portions of diethyl ether. The organic layers were combined and dried over sodium sulfate. The solvent was removed. This procedure afforded 2.32 g of a light brown oil. This oil was analyzed by NMR and GC (Varian 3300, DB-1 column, 20 m, 0.53 mm i.d.). The ^1H NMR spectral characteristics (JEOL JNM-A500, 500 MHz) were in good agreement with literature data, whereas the ^{13}C NMR data (JEOL JNM-LA400, 400 MHz) have not been reported previously. ^1H NMR ($CDCl_3$) δ: 2.05 (CH_3, s, 3H); 4.25–4.35 (OH, br, 1H); 5.07 (CH, s, 1H), and 7.29–7.38 (arom.-H, m, 5H). ^{13}C NMR ($CDCl_3$) δ: 25.3 (CH_3); 80.2 (CHOH); 127.4 (o-C-arom.); 128.8 (p-C-arom.); 129.1 (m-C-arom.); 138.0 (C1-arom.), and 207.2 (CO). The signals were assigned by the use of tables (34).

Asymmetric Synthesis of (1*R*,2*S*)-1-Phenyl-1,2-propanediol

Procedure

The asymmetric synthesis of (1*R*,2*S*)-1-phenyl-1,2-propanediol (**F**, Fig. 1) was performed by the $LiAlH_4$ reduction of the carbonyl group of the α-ketols obtained in the previously described synthesis, Fig. 7 (35). Because of the starting material used, it is known that the synthesis would afford all the four possible isomers. The determination of their structures was based on a combination of the GC equipped with a chiral column, molecular modeling, and ^1H NMR.

In a dry flask, under argon atmosphere, approximately 1.20 g (32 mmol) of $LiAlH_4$ and tetrahydrofuran (THF) were added. The glassware for the reactions was dried by heating under vacuum. The diethyl ether and the THF used were purified by distillation over Na/benzophenone under argon atmosphere. After cooling to approximately –90°C, a solution of 1.69 g of the oil obtained in the previous synthesis in THF was slowly added. The mixture was stirred and slowly heated to room temperature for 25 h. The flask content was poured into another flask with water under stirring and acidified with dilute hydrochloric acid. The products were extracted with three approximately 50 cm^3 portions of diethyl ether. The organic layer was washed with water and then dried over sodium sulfate. The solvent was removed. To remove all the THF and other volatile substances, the mixture was heated under vacuum. This procedure afforded 1.26 g of a light brown oil. This oil was analyzed by NMR (JEOL JNM-A500, 500 MHz), GC (Varian 3300, column DB-1, 20 m, 0.53 mm i.d.), and GC-MS (HP 5973, column HP-1, 15 m, 0.2 mm i.d., 0.25 μm film thickness, MS parameters: E.I. at 70 eV, scan range 35 to 600 a.m.u.). The spectral data were in agreement with the molecular structure of the target compound. Pair of diastereomers (1*R*,2*S*) and (1*S*,2*R*)-1-phenyl-1,2-propanediol: ^1H-NMR ($CDCl_3$) δ (ppm): 1.05 (CH_3, d, J = 6.4 Hz, 3H); 2.60–3.20 (OH, br, 1H); 3.97 (CH_3-C<u>H</u>OH-CHOHC_6H_5, qd, J = 6.4 and

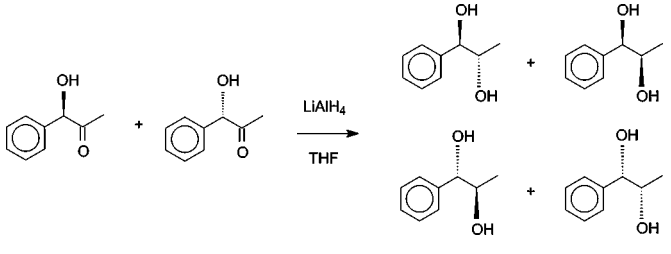

FIG. 7. Reaction scheme in the asymmetric synthesis of (1*R*,2*S*)-1-phenyl-1,2-propanonedione.

4.2 Hz, 1H); 4.64 (CH_3-CHOH-C<u>H</u>OHC_6H_5, d, J = 4.1 Hz, 1H); and 7.20–7.40 (arom.-H, m, 5H). Pair of diastereomers (1*R*,2*R*) and (1*S*,2*S*)-1-phenyl-1,2-propanediol: 1.03 (CH_3, d, J = 6.3 Hz, 3H); 2.60–3.20 (OH, br, 1H); 3.83 (CH_3-C<u>H</u>OH-CHOHC_6H_5, dq, J = 7.5 and 6.3 Hz, 1H); 4.32 (CH_3-CHOH-C<u>H</u>OHC_6H_5, d, J = 7.5 Hz, 1H); and 7.20–7.40 (arom.-H, m, 5H).

The minimum energy conformations for the two pairs of diastereomers ((1*R*,2*S*), (1*S*,2*R*)) and ((1*R*,2*R*), (1*S*,2*S*)) were determined by molecular mechanics calculations using Cache programme (15) and are presented in Fig. 8 for the major (1-hydroxy) product. Based on the obtained data, the hydrogen atoms attached to C_1 and C_2 in the minimum energy conformation of the major pair of diastereomers are in a *gauche* relationship. On the other hand, the same hydrogens in the minimum energy conformation of the minor pair of diastereomers have a *trans* relationship to each other. Thus, the coupling constant (J) between these two hydrogens in the ^{1}H NMR spectrum of the first pair should be smaller than that of the other pair, according to the Karplus equation (36). This conclusion was supported by the H^1 NMR data on (1R,2R)-1-phenylpropane-1,2-diol reported by Sharpless and co-workers (38). Considering this information, it was possible to find out, by integration of the signals of the protons in the ^{1}H NMR spectrum, that the ratio between the (1*R*,2*S*) and (1*S*,2*R*) and the (1*R*,2*R*) and (1*S*,2*S*) was approximately 76:24. This ratio was in good agreement with the ratio found by the authors of the reference (38) (80:20). So, it was known that the isomer (1*R*,2*S*) would be that obtained in larger amounts, followed by the (1*R*,2*R*) isomer and after these would come the (1*S*,2*R*) isomer, followed by the (1*S*,2*S*) isomer. With this knowledge it was possible to assign the four peaks due to the diols obtained by the analysis of the asymmetric synthesis product of the (1*R*,2*S*)-1-phenyl-1,2-propanediol. By this analysis it was also possible to determine the ratio between both pairs of diastereomers, which was found to be approximately 75 : 25.

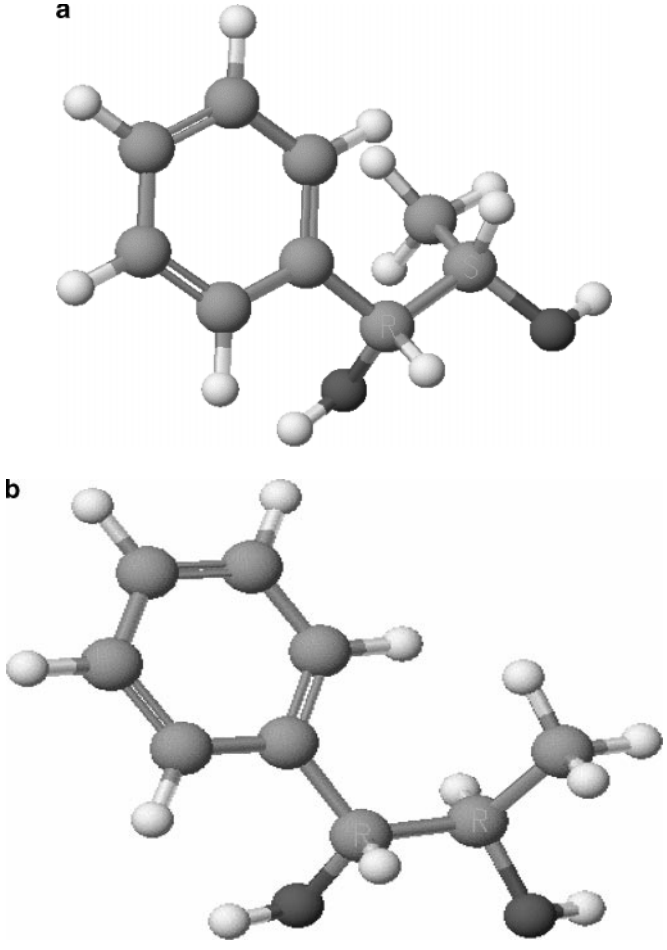

FIG. 8. The energy minimized conformations of (a) (1*R*,2*S*)-1-phenyl-1,2-propanediol and (b) (1*R*,2*R*)-1-phenyl-1,2-propanediol modeled with Cache program (15).

Synthesis of Racemic 1-Hydroxy-1-phenylpropanone

The synthesis of the racemic mixture of the 1-hydroxy-1-phenylpropanone was carried out by the method used in the synthesis of (*R*)-1-hydroxy-1-phenylpropanone (**B**, Fig. 1) by starting from the racemic mandelonitrile (Aldrich, technical grade) in order to make the calibration curve for gaschromatographic analysis. It was found out that some impurities in the racemic mandelonitrile gave acidic characteristics to this material. Hence, it was purified using an aqueous solution of sodium hydrogen carbonate. Then the protection of the hydroxyl group and the Grignard reaction were carried out as described previously. The procedure afforded a light brown oil, which was analyzed by ^{1}H NMR (JEOL NMR-LA400, 400 MHz), GC (Varian 3300, DB-1 column, 20 m, 0.53 mm i.d.), and GC-MS (HP 5890 series II, column DB-1, 25 m, 0.32 mm i.d., 0.25 μm film thickness, MS parameters: HP 5971-A, E.I. at 70 eV). The purity of the product, 1-hydroxy-1-phenylpropanone was 57.9% as determined by ^{1}H NMR analysis. 1-Hydroxy-1-phenylpropanone ^{1}H-NMR ($CDCl_3$) δ 2.09 (CH_3, s, 3H); 4.35 (OH, d, 1H); 5.10 (CH, d, 1H); and 7.27–7.43 (Ar.-H, m, 5H). 2-Hydroxy-1-phenylpropanone δ 1.5 (CH_3, d, 3H); 3.84 (OH, d, 1H); 5.13–5.20 (CH, m, 1H); 7.49–7.54 (Ar.-H, m, 2H); 7.61–7.66 (Ar-H, m, 1H); and 7.92–7.95 (Ar-H, m, 2H). The purity of the product was relatively low due to the technical quality of the starting material, mandelonitrile. During this purification, the other α-hydroxyketone (2-hydroxy-1-phenylpropanone) was formed. We believe that it happened via the α-ketol rearrangement since the mixture possibly contained small amounts of acid from the previous step. The purity of this compound was also determined by quantitative ^{1}H NMR to be 29.7%.

Synthesis of Racemic 2-Hydroxy-1-phenylpropanone

General Considerations

All operations with organometallic reagents were carried out in an argon atmosphere. Tetrahydrofuran was dried and distilled from Na/benzophenone prior to use. *n*-Butyllithium (Acros, 2.5 mol/dm^3 solution in hexane) was used as received. Products were confirmed by ^{1}H and ^{13}C NMR spectra recorded in $CDCl_3$ solution using a JEOL JNM-LA400 spectrometer and referenced against the residual protons of the deuterated solvent.

*Preparation of 2-Hydroxy-1-phenylpropanone (***D** + **E***, Fig. 1)*

2-Phenyl-1,3-dithiane was prepared from benzaldehyde (Baker) and propane-1,3-dithiol (Acros) as described previously (38). The racemic 2-hydroxy-1-phenylpropanone (**D** + **E**, Fig. 1) was prepared by lithiation of 2-phenyl-1,3-dithiane with *n*-butyllithium and the subsequent reaction with acetaldehyde followed by treatment with $HgCl_2/CaCO_3$ in aqueous MeOH (35). Distillation gave fairly pure 2-hydroxy-1-phenylpropanone as a yellow oil (bp. 84–86°C/0.5 mbar) that was purified by crystallization from diethyl ether at −30°C. The purity of 2-hydroxy-1-phenylpropanone was determined to be 95.8 % by quantitative ^{1}H NMR. ^{1}H NMR ($CDCl_3$, δ): 1.42 (d, CH3, J = 7.0 Hz, 3H); 3.80 (d, -OH-, J = 6.3 Hz, 1H); 5.14 (dq, -CO-CH-, J = 7.0 and 6.3 Hz, 1H); 7.61–7.56 (m, Ar–H, 3H); 7.92–7.88 (m, Ar–H, 2H). ^{13}C NMR ($CDCl_3$, δ): 22.22; 69.25; 128.59; 128.81; 133.91; 202.31.

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