

Enantioselective hydrogenation of exocyclic α,β -unsaturated ketones

Part III. Hydrogenation with Pd in the presence of cinchonidine

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Abstract

Cinchonidine as a chiral modifier was used in the hydrogenation of exocyclic α,β -unsaturated ketones with palladium black catalyst, producing the corresponding saturated ketones up to 54% optical purity (2-benzyl-1-benzosuberone) in toluene under 50 bar hydrogen pressure. The influence of different parameters (solvent, catalyst) on the optical yield was investigated. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Reduction of prochiral unsaturated substrates is an important method for the synthesis of chiral compounds. The enantioselective hydrogenation of the C=O group was widely studied [1], but the reduction of the C=C bond, especially that in exocyclic α,β -unsaturated ketones was less published [2,3].

There are two synthetically useful catalytic systems: tartaric acid modified Ni catalysts for enantioselective hydrogenation of β -ketoesters [4,5] and cinchona alkaloid modified Pt catalysts for reduction of α -ketoesters [6–9].

Besides platinum, cinchonidine modifies palladium in the hydrogenation of the double bond of C=C of (*E*)- α -phenylcinnamic acid [10–13]. Pd/TiO₂ catalyst

in the mixture of dimethyl formamide and water afforded 72% optical yield [14].

The Pd/TiO₂/cinchonidine system was the best in the hydrogenation of the double bond of C=C of 4-hydroxy-6-methyl-2-pyrone in acetonitrile with 85% enantioselectivity [15,16].

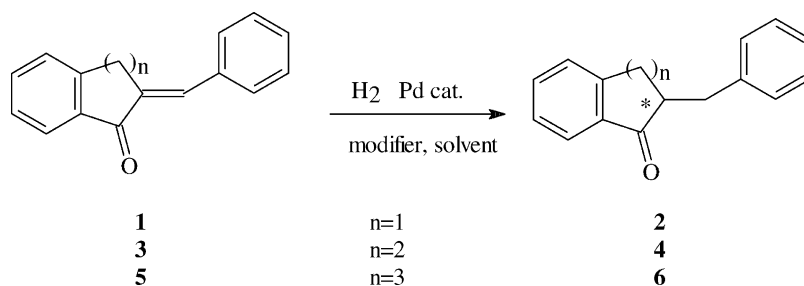
Another alkaloid, (–)-ephedrine was found to be effective modifier, or more correctly effective auxiliary in the hydrogenation of the double bond of C=C of (*E*)-2-benzylidene-1-tetralone over Pd/C in acetonitrile, with 36% optical purity and 82% yield [3].

Previously, we have reported on the enantioselective hydrogenation of exocyclic α,β -unsaturated ketones using Pd-on-carbon in the presence of (*S*)-proline as a chiral auxiliary with an enantiomeric excess of 20% under optimal conditions [3]. To improve the efficiency of the asymmetric hydrogenation several chiral modifiers were tested, the highest optical yield was achieved with cinchonidine.

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Scheme 1. The heterogeneous catalytic hydrogenation of (*E*)-2-benzylidene-1-indanone, (*E*)-2-benzylidene-1-tetralone and (*E*)-2-benzylidene-1-benzosuberone to the corresponding saturated ketones.

In the present work, the palladium catalysed hydrogenation of (*E*)-2-benzylidene-1-indanone (**1**) to 2-benzyl-1-indanone (**2**), (*E*)-2-benzylidene-1-tetralone (**3**) to 2-benzyl-1-tetralone (**4**) and (*E*)-2-benzylidene-1-benzosuberone (**5**) to 2-benzyl-1-benzosuberone (**6**) was investigated in order to find appropriate reaction conditions to obtain the highest enantioselectivity (Scheme 1).

2. Experimental

2.1. Materials

Compounds **1** and **3** were prepared according to the procedure described in [17], while **5** was synthesised as described in [18].

Pd black catalysts were prepared according to the following procedure: 9 mmol (3.0 g) K₂PdCl₄ was dissolved in 30 ml water and reduced at boiling point with 2.5 g HCOONa in 20 ml water. The pH value of the solution was adjusted to 9 by addition of KOH. The suspension was boiled for 1 h then cooled, the catalyst filtered and washed several times with distilled water until the water became neutral.

Pd/TiO₂ catalysts were prepared according to the following procedure: calculated amount of the K₂PdCl₄ was added to the aqueous suspension of the support. The pH value was adjusted to 11 by addition of KOH. The suspension was boiled for 1 h, then the reducing agent HCOONa (three times the stoichiometric amount) was added to the boiling mixture. After 30 min, the suspension was cooled, the catalyst was filtered and washed with distilled water.

The Rh/C catalyst was commercial product of Aldrich. Cinchonidine, cinchonine, quinidine and quinine were purchased from Fluka. Toluene, hexane, ethyl acetate, methanol, acetonitrile, dimethylformamide and acetic acid were supplied by Fluka.

2.2. Hydrogenations

The hydrogenations were carried out in a stainless steel autoclave (Technoclave) with magnetic stirrer at room temperature and at 50 bar hydrogen pressure. Before hydrogenation, the reaction mixtures were stirred under nitrogen (2–3 bar) for 10 min in the reaction vessel.

The working-up procedure of the reaction mixtures was the catalyst filtration and the removal of the solvent in vacuum. The residue was dissolved in dichloromethane and extracted with 5% HCl and distilled water. The organic phase was separated and dried over Na₂SO₄. After filtration, the solvent was removed in vacuum.

The product was analysed by HPLC, from these chromatography data conversion, selectivity and enantioselectivity values were calculated.

2.3. Analysis

The HPLC analyses were carried out on a Chiralcel OJ column (0.46 cm × 25 cm). The column contains silica gel as packing material coated with a cellulose derivative. The eluent was hexane/2-propanol 90:10 (v/v), the flow rate was 1.0 ml/min and the column pressure was 50 kg/cm². The UV absorbance was

measured at 249 nm. Enantiomeric excesses were calculated according to the following equation:

$$\text{e.e. (\%)} = \frac{[A] - [B]}{[A] + [B]} \times 100$$

where [A] is the concentration of major enantiomer and [B] the concentration of minor enantiomer.

3. Results and discussion

3.1. Effect of solvents

It is well known that in the catalytic hydrogenation the selectivity of the reaction, as well as the activity of the catalyst, can be influenced by using appropriate solvents [19]. The results of the hydrogenations of the substrate **5** in different solvents, over palladium black modified with cinchonidine are shown in Fig. 1. The effect of conditions was investigated with compound **5**, because it gave the highest e.e. values among the three unsaturated ketones.

The conversion and the chemoselectivity were 100% in all solvents. The highest enantioselectivity

45% was achieved over Pd black in toluene. It has to be mentioned that this solvent was not completely water-free. In hexane and ethyl acetate these values were among 37–35%, in acetonitrile, methanol and dimethyl formamide were lower, in acetic acid racemic product was formed.

3.2. Effect of the concentration of the modifier

The effect of the concentration of modifiers on the e.e. is shown in Fig. 2.

Our experience was that the e.e. values deviated in repeated experiments. It turned out that the reaction is very sensitive to the water content of toluene. Further on, the reactions were carried out in absolute toluene. The conversion and the chemoselectivity were 100% in all the cases. An enhancement of the enantioselectivity was observed with increasing amount of cinchonidine, it reached a maximum at 5% (w/w) modifier with respect to the catalyst. Increasing the modifier concentration above this value the optical purity decreased. These hints that not only modification but also poisoning of the catalyst surface occurs.

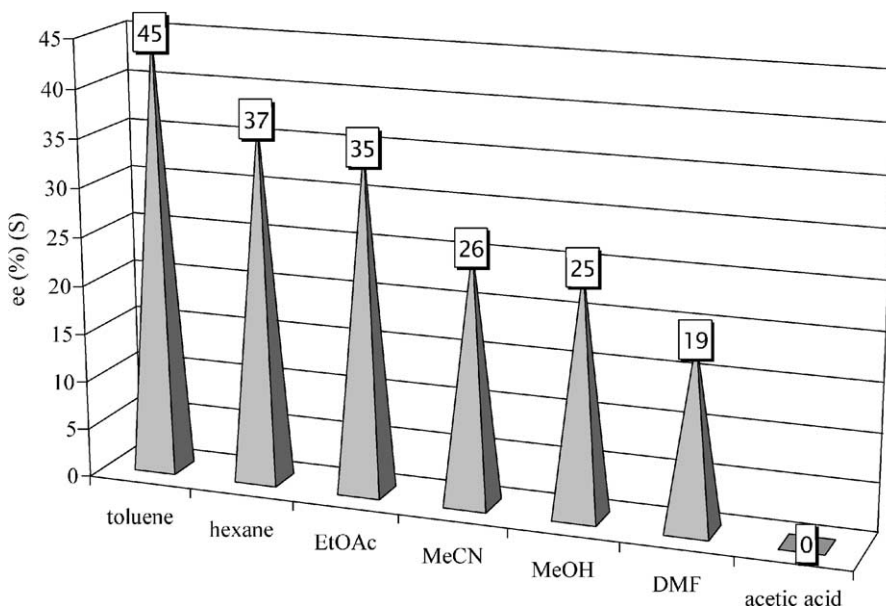


Fig. 1. The influence of different solvents on the enantioselectivity. Conditions: 0.5 g (*E*)-2-benzylidene-1-benzosuberone, 0.05 g Pd black, 20 ml solvent, 0.005 g cinchonidine, 2 h, 50 bar, 25 °C.

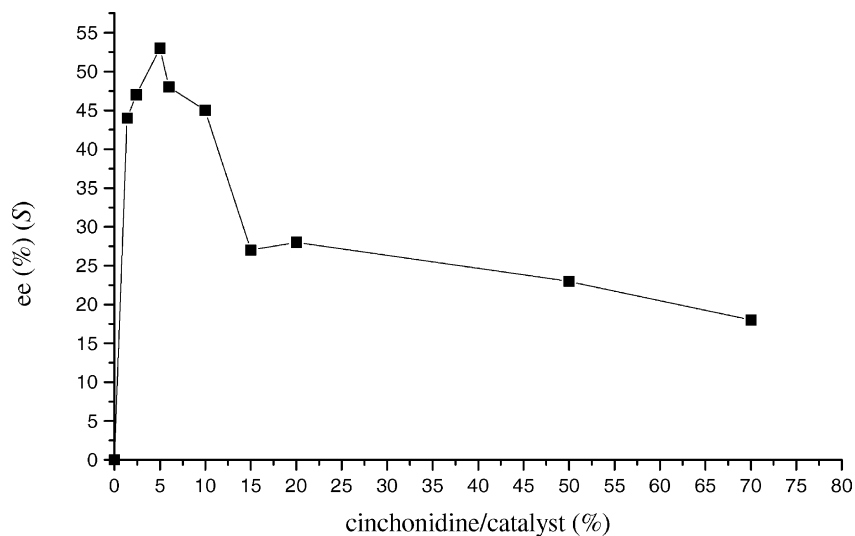


Fig. 2. The influence of the quantity of cinchonidine on the enantioselectivity. Conditions: 0.5 g (*E*)-2-benzylidene-1-benzosuberone, 0.05 g Pd black, 20 ml toluene, 2 h, 50 bar, 25 °C.

3.3. Conversion and reaction rate

The enantiomeric excess and the conversion as a function of the reaction time were illustrated in Fig. 3.

The hydrogenation was complete within 1.5 h and the chemoselectivity was 100%. The reaction rate was constant up to 90% conversion, this means that the reaction is zero order. The e.e. did not change with conversion.

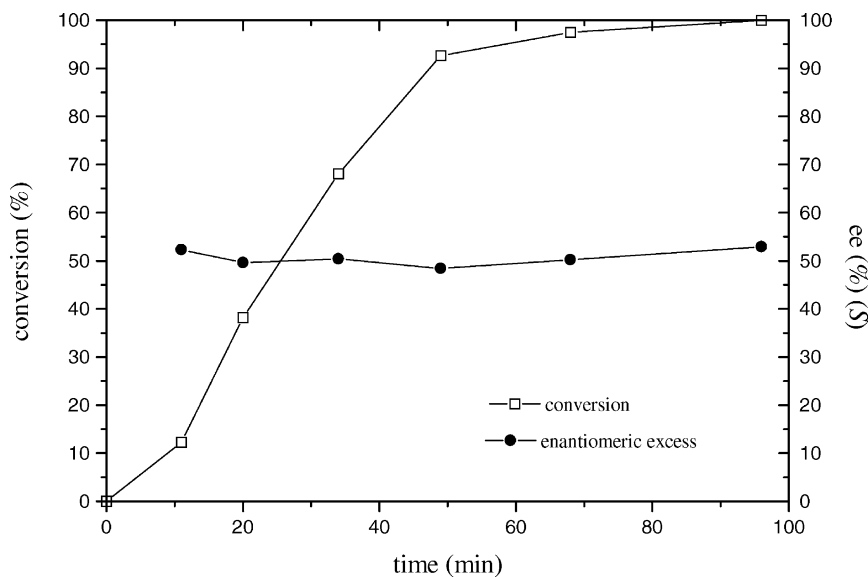


Fig. 3. The conversion and enantiomeric excess in the function of time. Conditions: 1 g (*E*)-2-benzylidene-1-benzosuberone, 0.1 g Pd black, 40 ml toluene, 0.005 g modifier, 50 bar, 25 °C.

Table 1
Effect of different catalyst on the enantioselectivity

Catalyst	Solvent	e.e. (<i>S</i> ; %)
Pd black	Toluene	53.7
Pd/TiO ₂	MeCN	37.1
Pd/TiO ₂	DMF/water	24.9
Pd/Al ₂ O ₃	MeOH	12.3
Pd/Al ₂ O ₃	Toluene	4.7
Ru/C	Toluene	–
Ru/C	MeOH	Chemoselectivity=0

Conditions: 0.5 g (*E*)-2-benzylidene-1-benzosuberone, 0.05 g catalyst, 20 ml solvent, 0.0025 g cinchonidine, 2 h, 50 bar, 25 °C.

3.4. Effect of different catalyst

The effect of the catalyst on the enantioselectivity in the hydrogenation of compound **5** in different solvents are summarized in Table 1.

The conversion and the chemoselectivity were 100% in all reactions. The highest enantioselectivity value 53.7%, was achieved over Pd black catalyst in toluene. The second best catalyst was Pd/TiO₂ in acetonitrile or dimethyl formamide/water, it gave somewhat smaller e.e. than the Pd black in toluene.

3.5. Effect of cinchona alkaloids

The most frequently used cinchona alkaloid is cinchonidine. The results of the reactions with other cinchona alkaloids are summarized in Table 2.

The cinchona alkaloid pairs (cinchonidine–cinchonine and quinidine–quinine) differ in absolute configuration on C8 and C9 atoms, cinchonidine, (dihydrocinchonidine) and quinidine results in the *S*, while cinchonine and quinine in the *R* configuration of the saturated ketones. As these modifier pairs are

Table 2
Effects of cinchona alkaloid on the enantioselectivity

Modifier	e.e. (%)	Configuration
Cinchonidine	53.7	<i>S</i>
Dihydrocinchonidine	52.3	<i>S</i>
Cinchonine	36.5	<i>R</i>
Quinidine	51.4	<i>S</i>
Quinine	36.7	<i>R</i>

Conditions: 0.5 g (*E*)-2-benzylidene-1-benzosuberone, 0.05 g Pd black, 20 ml toluene, 0.0025 g modifier, 2 h, 50 bar, 25 °C.

Table 3
Hydrogenation of **1** and **3** in different solvents and over different catalysts

Catalyst	Solvent	e.e. (%)	
		2 (<i>S</i>)	4 (<i>R</i>)
Pd black	EtOAc	0	0
Pd black	Toluene	4.4	2.5
Pd black	MeOH	9.6	5.6
Pd black	DMF/water	0	4.0
Pd/TiO ₂	MeCN	2.3	9.1

Conditions: 0.5 g substrate, 0.05 g catalyst, 20 ml solvent, 0.0025 g cinchonidine, 2 h, 50 bar, 25 °C.

quasi-enantiomers, they afford different enantioselectivity values.

3.6. Hydrogenation of **2** and **4** in different solvent and over different catalysts

Among the same conditions, described in Table 1, the substrates **1** and **3** were hydrogenated too, these results are summarised in Table 3.

The conversion and the chemoselectivity were 100% in all solvents. Comparing the corresponding data of Tables 1 and 3 the enantiomeric excess is much lower in the hydrogenation of **1** and **3** than in that of **5**.

The tendency is similar to that, which was achieved in the hydrogenation of these substrates with (*S*)-proline as chiral auxiliary over palladium [2].

4. Conclusion

Exocyclic α,β -unsaturated ketones were reduced to the corresponding saturated ketones over different catalysts in different solvents up to 53.7% enantioselectivity. The enantioselectivity is strongly dependent on the water content of the best solvent, toluene. The most efficient system was palladium black, cinchonidine modifier in toluene in the hydrogenation of the (*E*)-2-benzylidene-1-benzosuberone (e.e.: 53.7%). The optimal amount of modifier was 5% (w/w) with respect to the catalyst in this reaction.

The enantioselectivity was different for the five, six and seven-membered ring containing compounds among the same conditions. These significant

differences between the enantioselectivity values can be attributed to the different rigidity of the substrate molecules as mentioned in [4].

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