

A new chiral auxiliary in enantioselective hydrogenations: (–)-dihydrovinpocetine. Hydrogenation of ethyl pyruvate. II

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Abstract

A vinca-type synthetic alkaloid: (–)-dihydrovinpocetine functions as a chiral auxiliary in the enantioselective hydrogenation of the C=O group of ethyl pyruvate. Various catalysts, supports, solvents have been screened. The effect of modifier's concentration, acetic acid additive and of combined modifiers (+ dihydro-cinchonidine and -cinchonine) is described. The highest optical yield (30%) is obtained with a Pt on alumina catalyst. Mechanistic considerations and comparison with the known Pt/cinchona system have been made.

Keywords: Dihydrovinpocetine; Hydrogenation; Enantioselectivity; Chiral auxiliary; Ethyl pyruvate

1. Introduction

In the known heterogeneous catalytic enantioselective hydrogenations three main groups of chiral modifiers or auxiliaries are used: alkaloids, α -hydroxy acids and α -amino acids. In spite of the great number of chiral compounds, only a few of them are effective in heterogeneous catalytic systems. The most well-known examples are Ni catalysts modified with tartaric acid for the hydrogenation of β -keto esters [1] and Pt catalysts modified with cinchona alkaloids for the hydrogenation of α -keto esters [2].

In order to find a new chiral auxiliary with different or broader substrate specificity we have screened several vinca- and morphine-type alkaloids in the hydrogenation of various prochiral substrates [3]. A vinca-type alkaloid, dihydrovinpocetine (DHVIN I, Fig. 1) proved to be an effective chiral additive in the hydrogenation of both C=C and C=O double bonds.

Previously we reported the Pd mediated enantioselective hydrogenation of isophorone [4] and the preparation, structure and interaction with substrates of this vinca-type modifier compound [5].

In the present study, the hydrogenation of ethyl pyruvate using (–)-dihydrovinpocetine as

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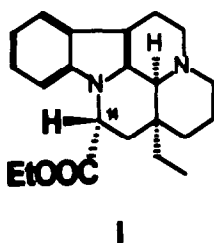


Fig. 1.

chiral auxiliary is discussed. Results on the influence of modifier concentration, type and support of the catalyst and the presence of acetic acid on the enantiomeric excess (ee %) and the rate of the hydrogenation are reported. On the basis of the combined use of cinchona- and the vinca-type modifiers considerations concerning the mode of action are made.

2. Experimental

2.1. Materials

The catalysts used were partly commercial products: 5% Pt/C Heraeus, Aldrich and Janssen, 5% Pt/Al₂O₃ Engelhard, Aldrich, Janssen. PtO₂ was the product of Degussa. Pt/SiO₂, Pt/TiO₂ were prepared as follows. The calculated amount of the catalyst precursor ((NH₄)₂PtCl₆) was added to the aqueous suspension of the support. The pH value of the solution was adjusted to 10–11 by addition of KOH. The suspension was boiled for 1 h then Na(HCOO) was added to the boiling mixture. After half an hour the suspension was cooled, the catalyst was filtered and washed with distilled water. Some catalyst samples (marked with "t") were heat-treated for three hours in a hydrogen stream at 400°C in a glass reactor, they were cooled down in nitrogen to room temperature.

Ethyl pyruvate, cinchonidine and cinchonine were supplied by Merck. Vinpocetine® [6] was supplied by Richter Gedeon Co. (–)-Dihydrovinpocetine was prepared in our laboratory by

catalytic hydrogenation of vinpocetine followed by separation of the epimers [5].

2.2. Hydrogenations

The hydrogenations were carried out in a Büchi BEP 280 autoclave equipped with a magnetically driven turbine stirrer and a gas-flow controlling and measuring unit. Before hydrogenation the reaction mixtures were stirred under nitrogen for 10 min in the reaction vessel. The reaction mixtures were worked up as follows. The catalyst was filtered and methanol was removed in vacuum. The residue was dissolved in dichloromethane and extracted with 7% KHSO₄ solution and dist. water. The organic phase was separated and dried over MgSO₄. After removal of the solvent the crude product was distilled in vacuum.

The reaction mixtures and the distilled products were analyzed by GC. The enantiomeric excesses were calculated from optical rotational data measured by a Perkin Elmer automatic polarimeter. The enantiomeric excess is based on the value of $[\alpha]_D^{20} = -11.4^\circ$ for optically pure (S)-(–)-ethyl lactate.

The reaction rates were calculated from the part of the hydrogen consumption curves between 10 and 40% conversion and expressed in 10^{–3} mol/min · g_{catalyst} units.

3. Results and discussion

The hydrogenation of ethyl pyruvate (Fig. 2) was carried out with different Pt catalysts in order to compare the effect of the two chiral modifiers: dihydrocinchonidine (DHCIN) and (–)-dihydrovinpocetine (DHVIN) which afforded an excess of the R-(+)-ethyl lactate and the S-(–)-lactate, respectively (Fig. 3).

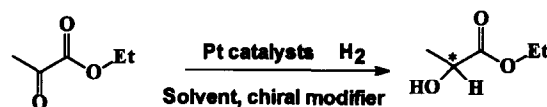


Fig. 2.

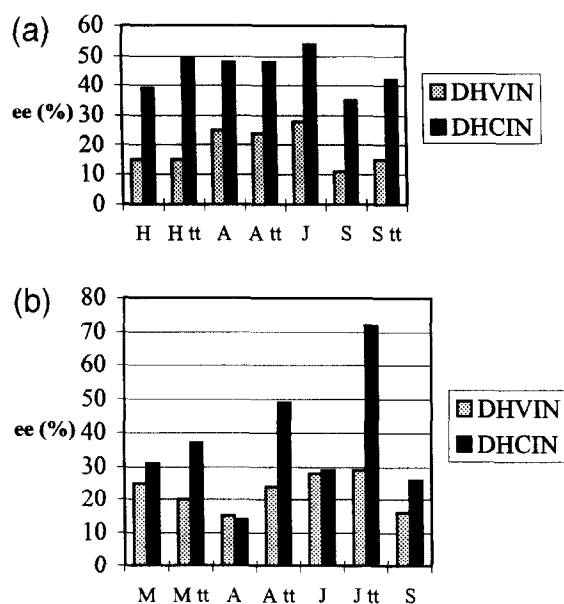


Fig. 3. (a) Enantioselectivities in pyruvate hydrogenation with Pt/C catalysts. (b) Enantioselectivities in pyruvate hydrogenation with Pt/Al₂O₃ catalysts. H = Heraeus, A = Aldrich, J = Janssen, M = Merck, S = prepared in our lab, tt = thermal-treated. Reaction conditions: 0.1 mol ethyl pyruvate, 0.1 g DHCIN, 0.2 g (–)-DHVIN+0.2 g acetic acid, respectively; solvent: with DHCIN 100 cm³ toluene; with DHVIN 100 cm³ methanol; temperature 25°C, pressure 10 bar, rpm: 1600–1800 min⁻¹.

The asymmetric induction observed with DHCIN (highest enantiomeric excess 72%) is much greater than that of DHVIN (highest ee 30%) with every catalyst studied. The modified carbon supported catalysts are more active, the alumina supported ones are more enantioselective, especially those which underwent thermal treatment. There was a rate enhancement effect upon addition of the alkaloids, but it was small

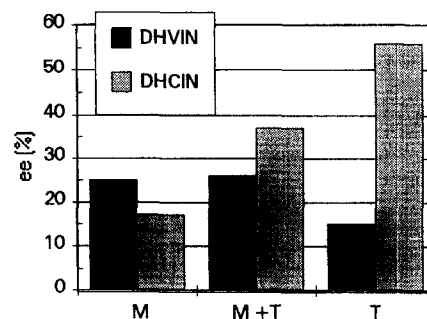


Fig. 4. Enantioselectivities in different solvents, reaction conditions: see Fig. 3. M = 100 cm³ methanol, T = 100 cm³ toluene, M+T = 50 cm³ methanol + 50 cm³ toluene.

in the case of DHVIN. Even with DHCIN the observed rate enhancements were smaller than those described previously.

The thermal-treatment exerted an effect on the performance of the catalysts, first of all on the alumina supported ones. However the preliminary impregnation of the catalysts with the solution of the modifier, DHVIN, had no significant change.

Silica and titania supported Pt catalysts and PtO₂ were also tested. The unsupported catalyst was very active, but gave lower enantioselectivity, the two supported ones had poor performance from both aspects.

The two chiral modifiers behave differently in methanol compared with toluene, as solvents (Fig. 4). In agreement with literature data [7] DHCIN has greater asymmetric effect in toluene than in methanol.

In order to reach the greatest effect of DHVIN, in addition to the protic solvent (for

Table 1

The effect of acetic acid additive on the ee and reaction rate of the hydrogenation of ethyl pyruvate

Catalyst	With acetic acid (0.2 g)			Without acetic acid		
	Conversion (%)	Reaction rate ^a 10 ³ (mol/min · g _c)	ee (%)	Conversion (%)	Reaction rate ^a 10 ³ (mol/min · g _c)	ee (%)
Pt/Al ₂ O ₃ (J) tt	95	0.9	26	77	2.1	8
Pt/Al ₂ O ₃ (E) tt	100	1.9	27	81	2.6	17
Pt/Al ₂ O ₃ (A) tt	23	0.6	16	37	2.4	9

^a Reaction conditions: 0.1 g catalyst: A = Aldrich, J = Janssen, E = Engelhard; tt = thermal-treated; 0.1 mol ethyl pyruvate, 0.2 g DHVIN, solvent: 100 cm³ methanol; temperature 25°C, pressure 45–50 bar, rpm: 1500 min⁻¹.

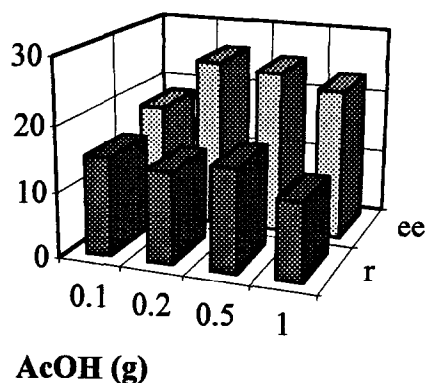


Fig. 5. The effect of the amount of acetic acid additive on the rate (10^{-3} mol/min·g_c) and ee (%) in the hydrogenation ethyl pyruvate. Reaction conditions: 0.1 g Pt/Al₂O₃ tt(E); 0.1 mol ethyl pyruvate, 0.1 g DHVIN, solvent: 100 cm³ methanol; temperature 25°C, pressure 45 bar, rpm: 1500 min⁻¹.

example methanol) a weak Brønsted acid (acetic acid) is needed. Upon adding acetic acid to the reaction mixture, in stoichiometric amounts with respect to the modifier, the enantiomeric excess increases significantly, but the reaction rate decreases (Table 1).

When a smaller amount of modifier (0.1 g) was used the rate decreasing effect of added acetic acid disappeared and the ee showed a maximum (Fig. 5).

Both the cinchona alkaloids and DHVIN are effective in relatively small concentrations. The values of ee and reaction rate as a function of

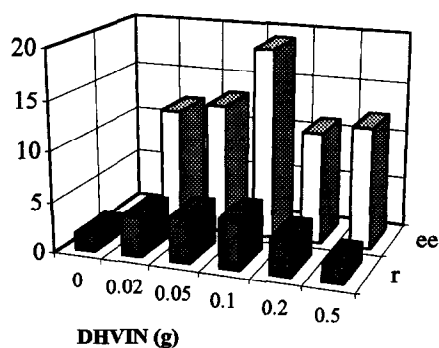


Fig. 6. Enantioselectivity (%) and reaction rate (10^{-3} mol/min·g_c) with Pt/C(A) catalyst. Reaction conditions: 0.1 g catalyst; 0.1 mol ethyl pyruvate, 0.2 g acetic acid (if DHVIN \geq 0.2 g amount of acetic acid = 0.5 g), solvent: 100 cm³ methanol, temperature 25°C, pressure 10 bar, rpm: 1500 min⁻¹.

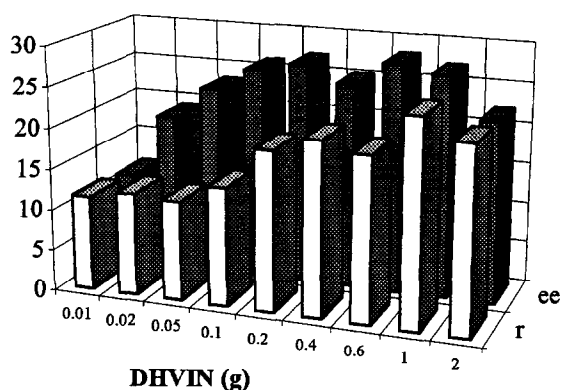


Fig. 7. Enantioselectivity (%) and reaction rate (10^{-3} mol/min·g_c) with Pt/Al₂O₃(E) catalyst.

the amount of the modifier are shown in Figs. 6 and 7.

The vinca-type alkaloid is effective also at low concentrations (< 0.3–0.6 mol% with respect to the substrate) and there is an optimum amount with respect to the enantioselectivity.

In every asymmetric reaction the question arises whether the increasing concentration of the chiral product and the change of the ratio of the substrate and the modifier with the conversion influence the enantioselectivity. The enan-

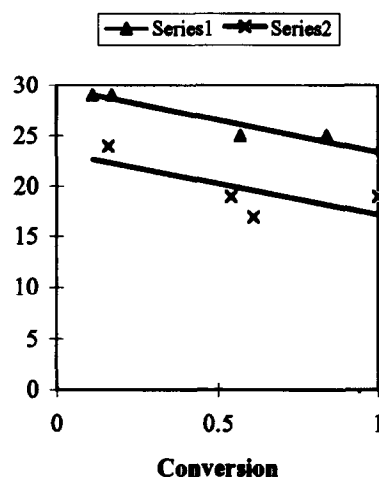


Fig. 8. Enantiomeric excess (%) versus conversion. Series 1: Pt/Al₂O₃, reaction conditions: 0.1 g catalyst, thermal-treated (Engelhard); 0.1 mol ethyl pyruvate, 0.1 g DHVIN, 0.5 g AcOH. Series 2: Pt/C, reaction conditions: 0.1 g catalyst (Aldrich); 0.1 mol ethyl pyruvate, 0.1 g DHVIN, 0.2 g AcOH. Solvent: 100 cm³ methanol, temperature 25°C, pressure 50 bar, rpm: 1500 min⁻¹.

tiomeric excess as a function of conversion was measured with two catalysts (Fig. 8). The ee decreases slightly. However, the extent of the change is not significantly greater than the error of the measurement.

The pressure has no detectable effect on the enantioselectivity, but increased the rate of the reaction (Table 2).

The hydrogenation of ethyl pyruvate in the presence of the cinchona-alkaloids or DHVIN is zero order with respect to the substrate.

According to the data of Table 3, the reaction is about first order with respect to the catalyst concentration. In this region of the catalyst concentration there seems to be no transport limitation of the reaction rate.

Analogous to the Pd mediated hydrogenation of isophorone in the presence of DHVIN [4], the combined effect of DHVIN and the two cinchona alkaloids was tested in the pyruvate hydrogenation. Using DHCIN (Fig. 9) alone the ee is about 55%, producing *R*-(+), with DHVIN alone it is 30%, producing *S*-(-)-ethyl lactate in excess among the same conditions. Dihydrocinchonine (DHCNN) (Fig. 10) also gives *S*-(-)-ethyl lactate in about 35% enantiomeric excess. It is evident from these Figs. (9 and 10) that at small added amounts of the cinchona alkaloids the latter ones take over the governing role in the asymmetric process.

On the basis of these experiments it could not be decided whether the phenomenon takes place only on the catalyst surface or there are also some preliminary interactions between the sub-

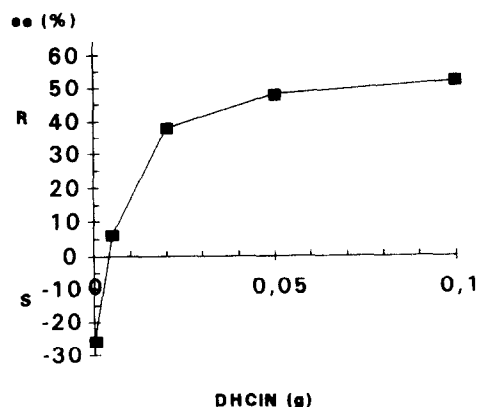


Fig. 9. Enantiomeric excess in the hydrogenation of ethyl pyruvate with DHVIN and increasing amount of DHCIN. Reaction conditions: 0.1 g Pt/Al₂O₃, thermal treated (Engelhard), 0.1 mol ethyl pyruvate, 0.1 g DHVIN + 0.5 g acetic acid + DHCIN, solvent 100 cm³ methanol, temperature 25°C, pressure 50 bar, rpm: 1500 min⁻¹.

strate and the modifiers in solution. Previously we reported circular dichroism measurements of the DHVIN modifier and the substrates isophorone and ethyl pyruvate in methanolic solution, which gave clear evidence of the interaction of these compounds in solution. The cinchona alkaloids were also tested, but the CD intensities of these compounds are much less than that of the DHVIN, and no changes in CD spectra upon adding the substrates to the modifier solution were observed.

Previous studies with the Pt/cinchonidine/ethyl pyruvate system [8] showed that the structure, dispersion, support, mode of preparation have great influence on the performance of the catalyst, first of all on the

Table 2
The effect of hydrogen pressure

Pressure (bar)	Conversion (%)	Reaction time (h)	ee (%)	Reaction rate ^a 10 ³ (mol/min · g _c)
2	91	7	22	2.8
10	100	6	19	4.8
40	100	7	19	3.3
50	100	5	19	6.9

^a Reaction conditions: 0.1 g Pt/C (Aldrich); 0.1 mol ethyl pyruvate, 0.1 g DHVIN, 0.2 g acetic acid, solvent: 100 cm³ methanol, temperature 25°C, rpm: 1500 min⁻¹.

Table 3
Effect of the concentration of the catalyst

Amount of catalyst (g)	Conversion (%)	Reaction time (h)	ee (%)	Reaction rate ^a 10 ³ (mol/min)	Reaction rate ^a 10 ³ (mol/min · g _c)
0.05	100	6	20	0.37	0.74
0.1	100	5	19	0.69	0.69
0.2	100	3	22	1.26	0.63

^a Reaction conditions: catalyst Pt/C (Aldrich); 0.1 mol ethyl pyruvate, 0.1 g DHVIN, 0.2 g AcOH; solvent: 100 cm³ methanol, temperature 25°C, pressure 50 bar, rpm: 1500 min⁻¹.

enantioselectivity and activity. The hydrogenations with the vinca-type alkaloid gave similar results: the support, the preparation method are important factors determining the catalyst properties. However the effect of the preliminary treatment in hydrogen on 400°C, and the impregnation with the solution of the modifier are not decisive factors.

TEM (transmission electron microscopy) pictures of the original and heat-treated alumina supported Pt catalyst (Janssen) showed no changes in the size of the metal particles (5–6 nm), but in the heat-treated catalyst there are more three-dimensional particles. According to the TEM pictures of the carbon supported Pt (Heraeus) before and after the thermal-treatment the dispersion increased (particle size 4 nm → 2–3 nm), and the distribution of the particle size became more homogeneous.

The reactions where dihydrocinchonidine was used demonstrated well these changes both in

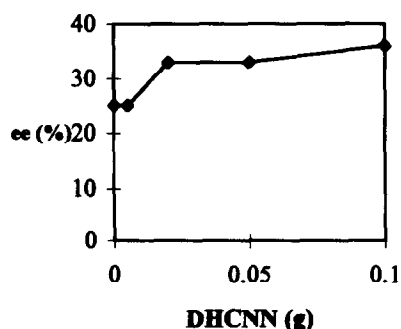


Fig. 10. Enantiomeric excess in the hydrogenation of ethyl pyruvate with DHVIN and increasing amount of DHCNN. Reaction conditions as for Fig. 9.

enantioselectivity (29% → 72%) and activity. It is probable that during the treatment in hydrogen at 400°C some precursors were reduced to metallic Pt of high degree of crystallinity. This can be more important in the cinchona-modified reactions than in the vinca-modified ones.

4. Conclusions

With (–)-dihydrovinpocetine as the chiral modifier, in addition to the asymmetric hydrogenation of the C=C double bond in isophorone (as previously reported [4]), the enantioselective reduction of the C=O group of pyruvate esters is possible with moderate enantioselectivities (up to 30%). There was rate enhancement effect too.

The best solvent of the reaction is methanol, the protonation of the modifier with a weak acid (acetic acid) is advantageous.

The modifier concentration–ee curves are similar to those observed with cinchonidine, at relatively low concentration the saturation value of ee is achieved. The much lower value of ee in comparison with the cinchonidine can be, at least partly, explained with the smaller rate enhancement produced by DHVIN. It has a small ‘ligand-accelerating’ effect.

However some interactions between the DHVIN and the substrates could be detected by CD in solution, the experiments of the combined use of the two different modifiers indicate that the most important in this asymmetric pro-

cess is the surface phenomenon, that is to say: the interactions in the catalyst/modifier/substrate system. Dihydrocinchonidine and dihydrocinchonine even at low molar ratio to DHVIN ($\approx 1:5$) determined the ee, hence we conclude that the determining step of the process involves molecules adsorbed on the surface.

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