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A new chiral auxiliary in enantioselective hydrogenations: (−)-dihydrovinpocetine. Part I. Hydrogenation of isophorone

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Abstract

A vinca-type synthetic alkaloid: (−)-dihydrovinpocetine is a promising chiral auxiliary in the enantioselective hydrogenation of the prochiral C=C bond of isophorone. Various catalytic metals and supports have been screened. The effect of acidic additives is described. The highest optical yield (38%) is obtained with a Pd black catalyst. Mechanistic considerations and comparison with the known Pt/cinchona system have been made.

Keywords: Chiral auxiliary; Dihydrovinpocetine; Enantioselectivity; Hydrogenation; Isophorone

1. Introduction

The known chiral auxiliaries for enantioselective hydrogenations can be classified into three main groups: alkaloids, hydroxy and amino acids. In spite of the great number of chiral compounds, only a few of them are effective chiral auxiliaries 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]. Premodification of the catalyst prior to the hydrogenation (Ni/tartrate) or in situ modification, i.e. simple addition of the auxiliary to the reaction mixture (Pt/cinchona) can ensure enantioselectivities up to 95%. Both systems are, however, effective only in the hydrogenation of C=O double bonds in a specific class of substrates.

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) proved to be an effective chiral additive in the hydrogenation of both C=C and C=O double bonds. The unsaturated compound, Vinpocetine **1** is a synthetic molecule which is used in the treatment of oxygen-deficiency of the brain [4].

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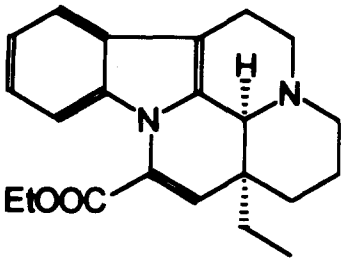

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In the present study, hydrogenation of isophorone using dihydrovinpocetine isomers as chiral auxiliaries is discussed. We report our results on the influence of modifier concentration, type and preparation of the catalyst and the presence of acids on the enantiomeric excess (% ee) and the rate of the hydrogenation. Considerations concerning the mode of action will be made. Our findings serve as a basis for more specific studies.

2. Experimental

2.1. Materials

The catalysts used were partly commercial products: 5% Pt/C Merck, 5% Pd/Al_2O_3 Aldrich, 5% Pd/$BaSO_4$ Aldrich, Pd powder Degussa and 10% Pd/C Selcat [5]. 10% Pd/TiO_2, 10% Pd/SiO_2, 10% Ru/C and 10% Ir/C were prepared as follows. The calculated amount of the catalyst precursor (K_2PdCl_4, $(NH_4)_2RuCl_6$ and $(NH_4)_2IrCl_6$, respectively) 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.

Pd black catalysts were prepared according to the following procedures: (type A) 18 mmol (6.0 g) K_2PdCl_4 was dissolved in 50 ml water and reduced at boiling point with 74 mmol (5.0 g) Na(HCOO) dissolved in 20 ml water. When the reduction was complete, the pH of the suspension was basic (pH 11); (type B) 18 mmol (6.0 g) K_2PdCl_4 was dissolved in 50 ml water and reduced with 53 mmol (2.0 g) $NaBH_4$; (type C) 53 mmol (6.0 g) K_2PdCl_4 was dissolved in 50 ml water and the pH of the solution was adjusted to 11 with KOH. The solution was reduced with hydrogen gas under atmospheric pressure; (type D) 20 mmol (6.53 g) K_2PdCl_4 was dissolved in 100 ml water and reduced with 41 mmol (2.8 g) Na(HCOO) at boiling point. When the reduction was complete, the pH of the suspension was acidic (pH 3). In all cases the catalyst was filtered and washed several times with distilled water.

Isophorone and cinchonidine were supplied by Merck. Vinpocetine® was supplied by Gedeon Richter Co. Dihydrovinpocetine was prepared in our laboratory by catalytic hydrogenation of Vinpocetine (10% Pd/C, MeOH, 6 bar, RT). The hydrogenation produced (−)- and (+)-dihydrovinpocetine **1a–1b** in 3:1 molar ratio shown by H^1-NMR spectroscopy. The two diastereomers could be partly separated by fractional crystallization from MeOH. The first fraction $\{[\alpha]_D^{20} = -1.05°$ (c 1, $CHCl_3$)$\}$ had a diastereomeric ratio of 92:8 and the second fraction $\{[\alpha]_D^{20} = +1.21°$ (c 1, $CHCl_3$)$\}$ had a diastereomeric ratio of 26:74. The best analytical separation and the determination of diastereomeric ratios could be achieved on a chiral HPLC column (Chiral-AGP, Sorensen-Buffer: isopropanol = 80:20). Samples taken from these two fractions were used as additives in the hydrogenation of isophorone.

2.2. Hydrogenations

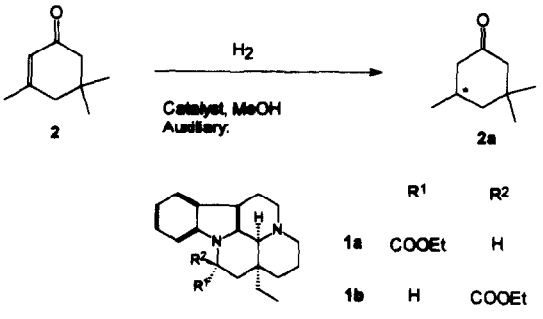
The hydrogenations were carried out in a conventional apparatus under atmospheric pressure or in a Büchi BEP 280 autoclave equipped with a magnetically driven turbine stirrer and a gas-flow controlling and measuring unit. Before hydrogenation the reaction mixtures were stirred under nitrogen for 10 min 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 dichlo-

romethane and extracted with 5% HCl and distilled water. The organic phase was separated and dried over $MgSO_4$. 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 $[\alpha]_D^{20} = +29°$ (neat) [6] for optically pure (*S*)-(+)-dihydroisophorone.

3. Results and discussion

Our investigations were carried out with the following model reaction:



The influence of the concentration of (−)-DHVIN **1a** on the ee. and the rate of the hydrogenation is depicted in Fig. 1. Only a small amount of the auxiliary is sufficient to reach the maximum level of ee. Enantioselectivity starts to decline when (−)-DHVIN is present in less than 0.3 mol% with respect to the substrate. Similar dependence of the ee on the modifier concentration was observed for the Pt/cinchona system [7]. This suggests that modification of the catalyst surface occurs. Saturation of the surface by the adsorbed auxiliary corresponds to the maximum level of enantioselectivity. However, enantioselection is coupled with a rate enhancement in the Pt/cinchona system. In our case, the rate of the hydrogenation drops rapidly upon addition of the auxiliary, therefore the ligand-accelerated mechanism applied for the Pt/cinchona system [8] cannot be operative.

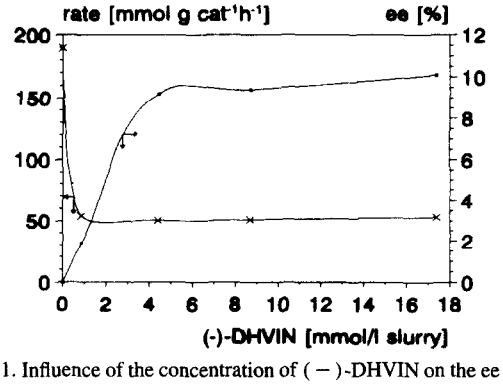


Fig. 1. Influence of the concentration of (−)-DHVIN on the ee and the initial rate. Conditions: 0.05 mol (7.0 g) isophorone, 0.2 g Pd/C, 25 ml MeOH, atmospheric pressure, 25°C.

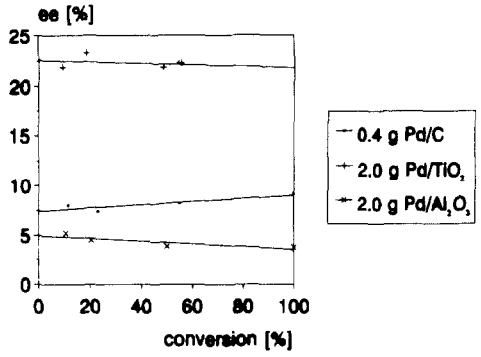


Fig. 2. Enantioselectivity versus conversion. Conditions: 0.2 mol (28.0 g) isophorone, 0.4 g (−)-DHVIN, 100 ml MeOH, 0.2–1.0 g AcOH, 6 bar, 25°C.

We have investigated how the degree of conversion affects the optical yield with three different catalysts. As is shown in Fig. 2, conversion has practically no effect upon optical yield. This is in agreement with results reported for the Pt/cinchona system in the hydrogenation of α-keto esters [9].

In a series of experiments hydrogenation of isophorone was carried out in the presence of both (−)-DHVIN and cinchonidine (CIN). The amount of (−)-DHVIN was kept constant while the amount of CIN was increased in each experiment. The change of ee versus concentration of CIN is depicted in Fig. 3. When only cinchonidine is added, (*S*)-(+)-dihydroisophorone is formed in 3.1% ee under the given reaction conditions. The observed ee (3.1%) at high concentration of CIN correlates with this value. Presumably, upon increasing the amount of cin-

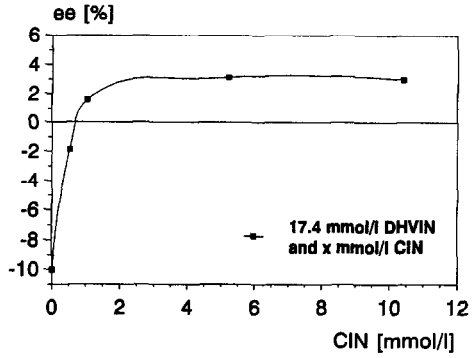


Fig. 3. Hydrogenation of isophorone in the presence of (−)-DHVIN and CIN. Conditions: 0.05 mol (7.0 g) isophorone, 0.2 g Pd/C catalyst, 25 ml MeOH, atmospheric pressure, 25°C.

Table 1
Hydrogenation of isophorone with different catalysts. Variation of the catalytic metal

Entry	Catalyst, amount (g)	(−)-DHVIN/ AcOH (g/g)	Conversion (%)	Reaction time (h)	ee (%)
1	Pd/C, 0.2	0.2/0.2	87	7.5	10 (*R*)
2 [a]	Pt/C, 0.2	0.2/0.1	57	7.0	1.9 (*R*)
3	Rh/C, 0.2	0.2/0.2	65	6.5	0.83 (*S*)
4 [a,b]	Ru/C, 0.5	0.2/0.1	76	7.0	0.30 (*S*)
5 [c]	Ir/C, 0.5	0.2/0.1	8.5	11.0	2.1 (*R*)

Conditions: 0.05 mol (7.0 g) isophorone, 25 ml MeOH, atmospheric pressure, 25°C.
[a] 100 ml.
[b] 40 bar.
[c] 50 ml MeOH and 6 bar.

chonidine, dihydrovinpocetine is displaced on the surface by cinchonidine due to the stronger adsorption of the latter. Although the concentration of DHVIN in solution is higher than that of CIN, the adsorbed auxiliary (CIN) being in excess on the surface of the catalyst controls the enantioselection. These results confirm that we are dealing with a surface phenomenon.

Different carbon supported catalytic metals have been screened in the hydrogenation (Table 1). The best ee was achieved with the Pd/C (Selcat Q) catalyst (Entry 1). The absolute configuration of the major enantiomer is influenced by the catalytic metal used. Rhodium and ruthenium give the (*S*)-(+)-dihydroisophorone in excess. The activity of rhodium and ruthenium are considerably lower thus necessitating a higher hydrogen pressure (40 and 6 bar respectively).

The effect of the support and the preparation method of the catalyst (Pd black) is summarized in Table 2 and Table 3. The structure of the catalyst has a strong influence on the optical yield which is characteristic of the modified catalytic systems (cinchona/Pt or tartaric acid/Ni). Cata-

Table 2
Hydrogenation of isophorone with different Pd catalysts. Variation of the support

Entry	Catalyst, amount (g)	(−)-DHVIN/ AcOH (g/g)	Conversion (%)	Reaction time (h)	ee (%)
1	Pd/C, 0.2	0.2/0.2	87	7.5	10 (*R*)
2	Pd/SiO_2, 0.5	0.2/1.0	84	8.0	9.6 (*R*)
3	Pd/TiO_2, 0.5	0.2/1.0	26	9.0	22 (*R*)
4 [a]	Pd/Al_2O_3, 0.5	0.2/1.0	100	8.0	11 (*R*)
5	$Pd/BaSO_4$, 0.5	0.2/1.0	91	8.0	16 (*R*)
6 [b]	Pd black, 0.3	0.2/1.0	84	8.0	38 (*R*)
7 [b]	Pd powder, 0.3	0.2/1.0	42	7.0	14 (*R*)

Conditions: 0.05 mol (7.0 g) isophorone, 25 ml MeOH, atmospheric pressure, 25°C.
[a] 100 ml MeOH and 6 bar.
[b] 100 ml MeOH and 40 bar.

Table 3
Hydrogenation of isophorone with different Pd black catalysts

Entry	Pd black type	Conversion (%)	Reaction time (h)	ee (%)
1	type A	84	8.0	38 (*R*)
2 [a]	type A	32	6.0	19 (*R*)
3	type B	65	6.0	24 (*R*)
4	type C	95	7.0	26 (*R*)
5	type D	67	6.0	27 (*R*)

Conditions: 0.05 mol (7.0 g) isophorone, 0.3 g Pd black, 0.2 g (−)-DHVIN, 1.0 g AcOH, 100 ml MeOH, 40 bar, 25°C. For the preparation method of different Pd black catalysts see Experimental part.
[a] The catalyst received thermal treatment prior to hydrogenation.

Table 4
Hydrogenation of isophorone. Variation of the acid

Entry	DHVIN	Acid	Amount of acid (g)	ee (%)
1	(+)	none	–	5.6 (*R*)
2	(−)	none	–	10.1 (*R*)
3	(+)	AcOH	0.2	5.8 (*R*)
4	(−)	AcOH	0.2	10.4 (*R*)
5 [a]	(+)	H_2SO_4	0.9	0.6 (*R*)
6 [a]	(−)	H_2SO_4	0.9	1.8 (*R*)
7	(+)	CF_3COOH	0.2	0.4 (*S*)
8	(−)	CF_3COOH	0.2	1.7 (*S*)
9	(−)	$(COOH)_2$	0.2	8.6 (*R*)
10	(−)	C_6H_5COOH	0.4	6.2 (*R*)
11 [b]	(−)	AcOH	15 ml	4.1 (*R*)

Conditions: 0.05 mol (7.0 g) isophorone, 0.2 g 10% Pd/C catalyst, 0.2 g DHVIN 25 ml MeOH, atmospheric pressure, 25°C.
[a] 35 ml MeOH. The pH of the solution was adjusted to 4.
[b] The hydrogenation was carried out in pure AcOH with 0.5 g Pd/TiO_2 catalyst.

lysts with very high dispersion (Pd/C, $D > 0.6$) or with very low dispersion (Pd powder, $D < 0.01$) give lower enantioselectivities. Similar observations were made with the cinchona/Pt system where Pt/Al_2O_3 catalysts with dispersion between 0.2 and 0.4 are optimal. For the hydrogenation of isophorone, Pd black catalyst gives the best enantioselectivities (up to 38%). The activity of Pd black and Pd powder is low which necessitates higher pressure in the hydrogenation.

The performance of Pd black is strongly dependent on its preparation method (Table 3).

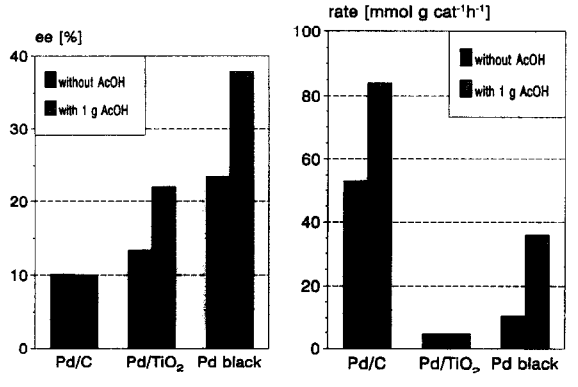


Fig. 4. Effect of the presence of acetic acid on the ee and the initial rate of the hydrogenation. Conditions: 0.05 mol (7.0 g) isophorone, 0.2 g (−)-DHVIN, 25°C. Pd/C: 0.2 g catalyst, 25 ml MeOH, atmospheric pressure. Pd/TiO_2: 0.5 g catalyst, 25 ml MeOH, atmospheric pressure. Pd black (type A): 0.3 g catalyst, 100 ml MeOH, 40 bar.

It is not clear whether the dispersion of the catalyst is the only factor which determines the enantioselectivity. Presumably, other factors such as support effect and organic residues remaining from the preparation process influence the adsorption of the auxiliary and thereby the optical yield. Characterisation of the different Pd black and supported Pd catalysts are in progress and might help to improve understanding of the phenomenon.

It is known for the cinchona/Pt system that carboxylic acids have a positive influence on the enantioselectivity of the hydrogenation, both as additives and as solvents. The best results are observed in acetic acid (up to 95% ee) in the hydrogenation of ethyl pyruvate [10].

We have also investigated the effect of acids with the dihydrovinpocetine/Pd system. Screening experiments with different substrates [3] showed that acetic acid has a positive influence on the ee in the hydrogenation of both ethyl pyruvate (reduction of C=O double bond) and isophorone. In a more detailed study, we used different acids (Table 4) either as additives (Entries 3–10) or as solvents (Entry 11).

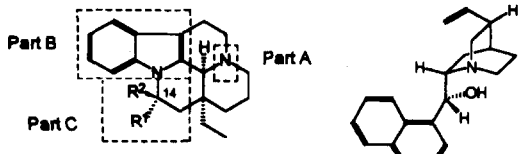
The hydrogenations were carried out with Pd/C or Pd/TiO_2 catalyst using (+)- or (−)-dihydrovinpocetine. With the exception of acetic acid, the presence of all acids leads to a decrease of the enantioselectivity. The extent of the effect depends on the strength of the acid. It is remarkable that with trifluoracetic acid both the (+)- and (−)-dihydrovinpocetine produce the (*S*)-(−)-dihydroisophorone in low optical purity.

The results obtained upon addition of acetic acid with three different palladium catalysts are depicted in Fig. 4. The presence of acetic acid leads to an increase in ee with both Pd/TiO_2 and Pd black catalysts. Interestingly, the ee is only slightly effected by the addition of acetic acid with the Pd/C catalyst. It is also clear that an increase in ee is not necessarily accompanied by an enhancement of the rate of the hydrogenation. We do not understand at the moment the exact role of acids in the hydrogenation. Presumably, acids can exert their effect in two ways: (i) protonation of the basic nitrogen in the dihydrovinpocetine or

(ii) modification of the surface of the catalyst by adsorption or by removal of organic residues remaining from the preparation process. These effects determine the change of ee and rate upon addition of acids.

3.1. Mechanistic considerations

The results obtained upon varying the amount of auxiliary suggests that dihydrovinpocetine exerts its effect by adsorption on the surface of the catalyst, i.e. an in situ modification occurs. Although the activity of the modified catalyst is lower, hydrogenation of isophorone proceeds with considerable enantioselection on the modified surface. The available results allow only very limited statements on the mode of action of the system. Considering the multifunctionality of dihydrovinpocetine, the structure of the molecule can be divided into three parts having separate function in the hydrogenation.



	R^1	R^2
1a	COOEt	H
1b	H	COOEt

3

The strong effect of acids on the enantioselectivity suggests that the basic nitrogen atom in dihydrovinpocetine ('Part A') might be responsible for the interaction with the substrate. There is an interesting parallel to the Pt/cinchona system, in which the basic nitrogen atom of the quinuclidine part is thought to have a similar role [9].

The indole ring ('Part B') might be responsible for the interaction with the surface of the catalyst. In the Pt/cinchona system the modifier (cinchonidine **3**) is anchored to the surface by a quinoline ring [9].

Enantioselectivity is sensitive to structural changes in 'Part C' of dihydrovinpocetine but the effect is not uniform. Although the two diastereomers of dihydrovinpocetine **1a**, **1b** differ in absolute configuration at C14, they give similar enantioselectivity. In contrast, our earlier investigations showed that vincamine (R^1: COOMe, R^2: OH), in which the hydrogen atom is replaced by a hydroxyl group at C14, has no enantioselective effect in the hydrogenation of isophorone [3]. It is probable that structural changes at any part of the molecule can influence its adsorption equilibrium and thereby the optical yield. Investigations aimed to obtain more information about the modifier/substrate/catalyst interactions are in progress and the results will be published in forthcoming papers.

4. Conclusions

Dihydrovinpocetine isomers **1a–1b** are promising chiral auxiliaries in the enantioselective hydrogenation of isophorone. The auxiliaries are used in a catalytic amount with respect to the substrate. The enantioselectivity is strongly dependent on the type of catalytic metal, the support and the preparation method of the catalyst. The best enantioselectivities (up to 38%) can be obtained with a Pd black catalyst. The effect of acidic additives is not uniform and depends on their strength and the type of the catalyst. Further investigations are required in order to provide an explanation for these empirical findings. This could then lead to further optimalization of the enantioselectivities.

Acknowledgements

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