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(*S*)-α,α-Diphenyl- and (*S*)-α,α-dinaphthyl-2-pyrrolidinemethanol as chiral modifiers in asymmetric heterogeneous catalytic hydrogenation of isophorone

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Abstract

The use of DPPM and DNPM as chiral modifiers in asymmetric heterogeneous catalytic hydrogenation of isophorone is reported. The effect of solvents and the concentration of reactant, modifiers and catalysts on the enantioselectivity are described. Circular dichroism spectroscopy was used to detect the interaction between the chiral modifier and the substrate.

Keywords: (*S*)-α,α-Diphenyl-2-pyrrolidinemethanol; (*S*)-α,α-Dinaphthyl-2-pyrrolidinemethanol; Chiral modifiers; Hydrogenation; Enantioselective

1. Introduction

Enantioselective reactions can be carried out with heterogeneous catalysts in principle by adding chiral compounds to the reaction mixture. Were these compounds added in stoichiometric amount, they are called chiral additives or auxiliaries; if they are present in catalytic amount, they are called chiral modifiers. The most studied precious metal catalysed reaction is the enantioselective hydrogenation of ethyl pyruvate to ethyl lactate on platinum catalysts modified with cinchona alkaloids, originally reported by Orito and Imai [1]. This effect is highly specific to the reactant, modifier, catalyst system, a behaviour that is characteristic for enzymatic reactions [2]. There are special requirements either for the modifier or the substrate.

Cinchona alkaloids were used as chiral modifiers in other catalytic reductions, like the enantioselective hydrogenation of (*E*)-α-phenylcinnamic acid [3], trifluoroacetophenone [4], 2-methyl-2-pentenoic acid [5] etc. Another alkaloid, the (−)-dihydroapovincaminic acid ethyl ester ((−)-DHVIN) was found to be effective modifier in the hydrogenation of the C=C bond of isophorone [6] and C=O bond of ethyl pyruvate [7].

As a result of the extensive work with modified reactions, it has turned out that the chiral modifier should possess two important properties in order to achieve significant enantioselectivities: being capable of anchoring on the catalyst surface and of interacting with the substrate [8]. In (−)-DHVIN and cinchonidine (CD) the basic N atoms were found to be responsible for the interaction with the substrate [9,10], while

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the indole ring of (−)-DHVIN [9] and the quinoline ring of CD [10] might be the anchoring parts.

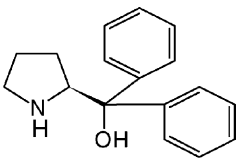
Baiker and co-workers [11] synthesised new, structurally simple chiral aminoalcohol modifiers, which possessed the crucial structural parts mentioned above (aromatic ring and basic nitrogen) and tested them in the hydrogenation of ethyl pyruvate. The (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl) ethanol was found to be the most effective modifier. It was advantageous for enantioselectivity if the modifier possessed a condensed aromatic ring as large as possible [12]. It means that if the modifiers have phenyl, naphthyl or anthracenyl moiety, the last is the most efficient.

Based on these findings, in order to broaden our knowledge on heterogeneously catalysed enantioselective hydrogenation reactions, we have tested the (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (DPPM) (Scheme 1) as modifier in the hydrogenation of C=C bond of isophorone.

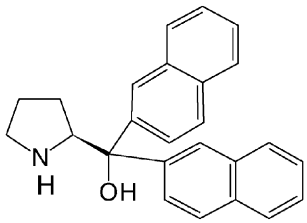
This molecule has already been used in the homogeneous enantioselective catalytic reduction of prochiral ketones, such as acetophenone and pinacolone [13–15].

The synthesis of this chiral compound is based on (*S*)-proline, which proved to be a good chiral auxiliary in asymmetric heterogeneous catalytic hydrogenations [16]. We supposed that the formerly mentioned phenomenon is valid in this case also, namely that the larger anchoring group gives higher asymmetric induction. In order to check it, (*S*)-α,α-dinaphthyl-2-pyrrolidinemethanol (DNPM) comprising two naphthyl rings instead of two phenyl rings was also synthesised (Scheme 2).

Present study is focused on the effect of the parameters, which are important for the catalytic performance: nature of solvent, concentration of the reactant, the modifiers and the catalyst. The interaction of DNPM chiral modifier with the substrate isophorone was detected with circular dichroism spectroscopy.



Scheme 1. DPPM.



Scheme 2. DNPM.

2. Experimental

2.1. Materials

Pd black catalysts were prepared according to the following procedure: 18 mmol (6.0 g) K_2PdCl_4 was dissolved in 100 ml water and reduced at boiling point with 36 mmol HCOONa dissolved in 20 ml water. The pH of the solution during the preparation was basic, and the whole amount of the reducing agent (HCOONa) was added at the beginning of the reaction. Isophorone was supplied by Merck. It was distilled in vacuum before use. DPPM and DNPM were prepared as described in [17].

2.2. Hydrogenation

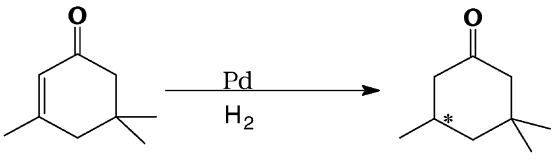
The hydrogenation of isophorone was carried out at 25 °C and under 50 bar hydrogen pressure in a stainless steel autoclave (Technoclave). Before the hydrogenation, the reaction mixtures were stirred under nitrogen for 10 min in the reaction vessel.

2.3. Analysis

The reaction mixtures were analysed with a gas chromatograph equipped with a β-cyclodextrine capillary column (analysis temperature: dihydroisophorone at 110 °C) and FID. The chromatograms were recorded and peak areas were calculated with Chromatography Station for Windows V1.6 (DataApex Ltd., Prague). Enantiomeric excess was defined as:

$$\text{ee}(\%) = \frac{[\text{R}] - [\text{S}]}{[\text{R}] + [\text{S}]} \times 100$$

Circular dichroism spectra were recorded on a D JASCO J-810 instrument. The cell length was 1 cm.



Scheme 3. Hydrogenation of isophorone.

3. Results and discussion

3.1. Catalytic tests

In the presence of DPPM and DNPM, the hydrogenation of C=C bond of isophorone (Scheme 3) resulted in an excess of the (*S*) enantiomer.

Table 1 shows results obtained in different solvents with DPPM and DNPM modifiers over Pd black catalyst.

The modifier with two naphthyl rings (DNPM) provided slightly lower optical purity by about 3–8%. In accordance with the enantioselective hydrogenation of (*E*)-α-phenylcinnamic acid [17] and isophorone [18], polar solvents and solvent mixtures were found to be advantageous. Now the highest asymmetric effect was perceived in *N*,*N*′-dimethylformamide (DMF) with DNPM and in methanol–water solvent mixture with DPPM. It is worth noting that water is a poor solvent for isophorone and two phases were present during reaction. Apolar solvents like toluene resulted in low ee. It is an interesting phenomenon that the presence of water in methanol increased the enantioselectivity of the reaction modified with DPPM, but it did not make any change in the case of DNPM.

Table 1
Influence of solvent on enantioselectivity and conversion[a]

Solvent	Conversion (%)		Enantioselectivity (%)	
	DPPM	DNPM	DPPM	DNPM
MeOH	100	42	23	20
DMF	100	69	33	25
CH_3CN	100	80	23	15
Toluene	100	70	14	8
H_2O	92	58	15	9
MeOH–H_2O 1:1	100	49	40	21

[a] Reaction conditions: 0.01 mol isophorone, 0.14 mmol modifier, 0.05 g Pd black, 10 ml solvent, $p = 50$ bar, $T = 25\,^{\circ}C$. Reaction time: 4 h.

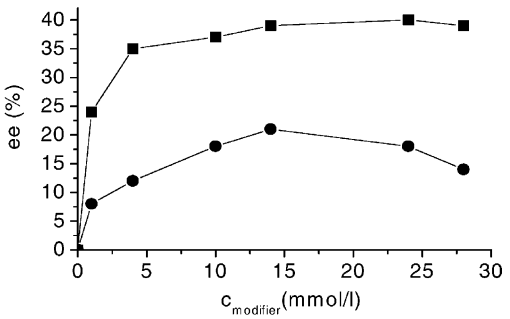


Fig. 1. Enantioselectivity as a function of DPPM (■) and DNPM (●) concentration. Reaction conditions: 0.01 mol isophorone, 0.05 g Pd black, 10 ml MeOH–water 1:1, $p = 50$ bar, $T = 25\,^{\circ}C$. Reaction time: 4 h.

The modified reaction is slower than the unmodified (racemic) hydrogenation. DPPM decreased the reaction rate in a smaller extent than DNPM. The effect of the concentration of modifiers on the ee is depicted in Fig. 1.

Both hydrogenation reactions were carried out in the methanol–water solvent mixture. In the presence of DPPM, an enhancement of the enantioselectivity was observed with increasing amount of modifier and reached a limit at 1.4 mol% with respect to the substrate. Increasing the modifier concentration above this value the optical purity slightly decreased. DPPM provided 19–20% higher ee than DNPM at this maximum. For comparison, in the same catalytic reaction the optimal value of the (−)-DHVIN/isophorone ratio was 0.3 mol% (ee 55%) [9], while 3 mol% CD/reactant ratio (highest ee 72%) was found in the Pd catalysed enantioselective hydrogenation of α- and β-substituted cinnamic acid derivatives [3,19].

The influence of the amount of catalyst on the enantiomeric excess and conversion is summarised in Table 2.

The reactions with DNPM were conducted with lower modifier concentration than the optimum value, even this amount of the modifier decreased the reaction rate remarkably. However, the optical purity was hardly affected by the amount of catalyst. Only a small drop in selectivity at very low catalyst loading was observed. This means that the enantiodifferentiation is not a purely surface dependent phenomenon.

The reaction rates were proportional with the amounts of catalyst. It indicates that the surface

Table 2
The effect of catalyst amount on the conversion and ee[a]

Amount of Pd black catalyst (g)	Reaction time (h)	Conversion (%)		ee (%)	
		DPPM	DNPM	DPPM	DNPM
0.05	2	100	90	39	8
0.025	4	100	93	39	5
0.015	4	96		35	

[a] Reaction conditions: 0.01 mol isophorone, 10 ml MeOH–H_2O 1:1, 0.14 mmol DPPM, 0.014 mmol DNPM, $p = 50$ bar, $T = 25\,^{\circ}C$.

chemical reaction is essential in the determination of the overall reaction rate. Therefore the reaction rate of unmodified and DPPM modified reactions as a function of conversion was investigated (Fig. 2).

The unmodified reaction seems to be diffusion controlled. Under standard conditions, the initial rate of H_2 consumption of the modified reaction was lower by a factor of 3.3 (0.15 and 0.5 bar H_2/min, respectively). A similar retarding effect of the chiral modifier was observed in the enantioselective hydrogenation of isophorone/(−)-DHVIN [9], (*E*)-α-phenylcinnamic acid/CD [3] and 2-methyl-2-pentenoic acid/CD [5].

Fig. 3 represents the influence of substrate concentration on the optical yield. In all cases, the modifier/substrate molar ratio was the optimal 1.4 mol%.

Reactant concentration in the range 0.5–2 mol/l had only a minor influence on ee. There is a slight optimum of enantioselectivity at 1 mol/l concentration of isophorone. Above the maximum, the increase of

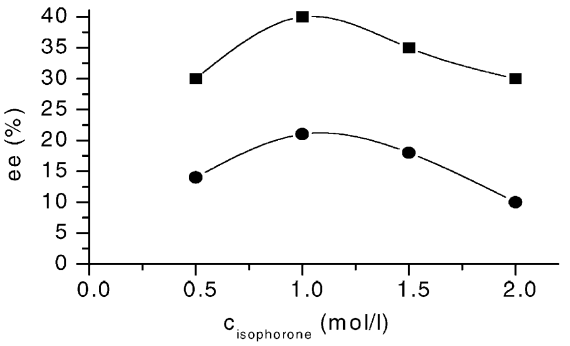


Fig. 3. Influence of substrate concentration on the ee of DPPM modified (■) and DNPM modified (●) reactions. Reaction conditions: 1.4 mol% DPPM/isophorone, 0.05 g Pd black, 10 ml MeOH–H_2O 1:1, $p = 50$ bar, $T = 25\,^{\circ}C$.

reactant concentration caused a remarkable decrease in selectivity with DNPM, but smaller with DPPM.

It was also investigated how the optical yield was affected by the degree of conversion in the DPPM modified reaction since it is important from practical as well as mechanistic point of view (Fig. 4).

It was found that the ee does not change at all until completion of the reaction. Our result shows that the Pd black/DPPM catalyst is quite stable under these conditions. This finding is in contrast to many reports on modified Ni catalysts, where a strong decrease in the optical yields was experienced at high conversions [17,20–22]. Product inhibition and a racemic hydrogenation at high conversion, as proposed by Nitta

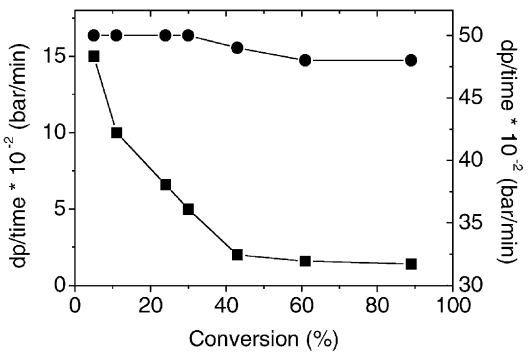


Fig. 2. The reaction rate of unmodified (●) and DPPM modified (■) reactions as a function of conversion. Reaction conditions: 0.01 mol isophorone, 0.14 mmol DPPM, 0.05 g Pd black, 10 ml MeOH–H_2O 1:1, $p = 50$ bar, $T = 25\,^{\circ}C$.

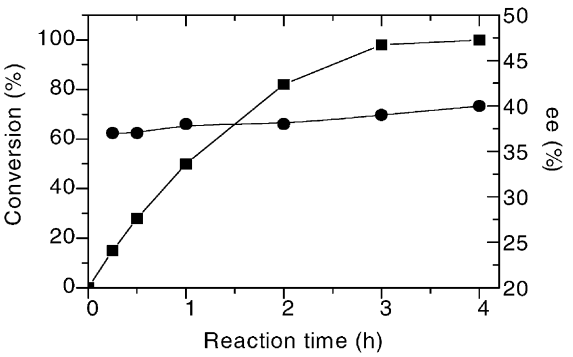


Fig. 4. Enantioselectivity (●) and conversion (■) as a function of reaction time. Reaction conditions: 0.01 mol isophorone, 0.14 mmol DPPM, 0.05 g Pd black, 10 ml MeOH–H_2O 1:1, $p = 50$ bar, $T = 25\,^{\circ}C$.

et al. [22] were not observed with our catalytic system. Other catalytic systems, where the optical yield remained constant throughout the whole reaction have also been described [23,24].

3.2. Interaction between the substrate and modifier

Generating differential spectrum is a sensitive method for detecting and recording changes in the CD spectrum associated with a change in the chromophore, in solvent perturbation or chemical reaction.

The CD spectrum of DNPM was recorded in methanolic solution ($c = 10^{-5}$ mol/dm^3). Thereafter the spectrum of DNPM and isophorone mixture (concentration of DNPM/isophorone = $10^{-5}/10^{-4}$ mol/dm^3) was recorded again in methanol. Finally, differential spectrum of the solution of DNPM and the solution containing DNPM and isophorone was composed.

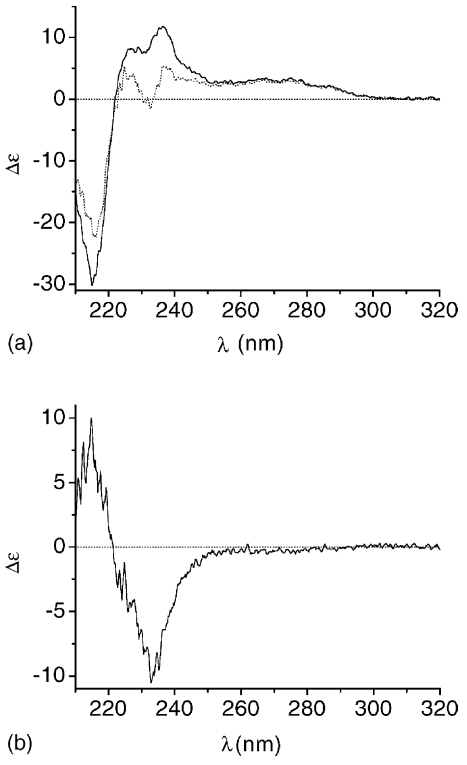


Fig. 5. (a) CD spectra of DNPM (–) and of DNPM and isophorone in great excess (···); (b) differential spectrum of DNPM with substrate in 10/1 molar ratio to the modifier, minus of DNPM without substrate.

This method was not applicable with DPPM modifier since the absorbance of isophorone in 10^{-5} mol/dm^3 concentration was 1, while the modifier gave an adequate signal ($A \sim 0.8$) only in 10^{-3} mol/dm^3 concentration. Mixing the substrate and modifier in equal quantity, the recorded spectrum was too noisy.

Measuring the spectrum of DNPM between 210 and 320 nm, it shows the presence of a positive Cotton effect containing vibrational fine structure in the 230–240 nm region as well as a more intense negative Cotton band near 215 nm. Both Cotton effects are due to aromatic transitions, since only the aromatic ring absorbs in the region above 200 nm. On the addition of excess isophorone to the solution of DNPM, the intensity of the bands and the shape of positive Cotton band is altered (Fig. 5a). These alterations can be observed by preparing the differential spectrum (Fig. 5b).

In the differential spectrum, there appear a positive and a negative Cotton band. The appearance of these bands is consistent with the interaction of DNPM and isophorone. The established interaction between the molecules of the substrates and the modifier influences the original electron transitions of the modifier.

4. Conclusions

Between the synthetic DPPM and DHVIN and the natural CD, there are similarities: the basic amine function in a rigid chiral environment and an aromatic ring system. It can be assumed that the basic, secondary N atom in the less flexible pyrrolidine ring of DPPM is responsible for interaction with the reactant.

Comparing the naphthyl, quinolyl, or indolyl groups of other modifiers, the two separate phenyl groups can provide only less strong anchoring effect of the chiral modifier on the metal surface. It was supposed that the modifier DNPM with two naphthyl groups had stronger anchoring effect, but it gave lower optical purity. We think that the two naphthyl groups on the same carbon atom make the molecule too bulky, thus weakening the interaction of the modifier with the catalyst surface.

The DPPM proved to be an acceptable chiral modifier in the hydrogenation of C=C bond of isophorone, the best ee was 40% in methanol–water 1:1 solvent mixture.

The example of DPPM and DNPM has the significance in broadening the scope of chiral modifiers and improving our knowledge about the structural parts needed for asymmetric induction.

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