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(*S*)-Proline based chiral modifiers

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Abstract

(*S*)-Proline esters and amides containing condensed aromatic rings were synthesised in order to use them as chiral modifiers in the enantioselective heterogeneous catalytic hydrogenation of isophorone and ethyl pyruvate. The (*S*)-proline 2-(2-naphthyl)-ethyl ester resulted in 23% enantiomeric excess of (*S*)-dihydroisophorone in methanol. 5% optical purity was obtained with the (*S*)-proline 3-ethyl-indolamide in the hydrogenation of ethyl pyruvate in acetic acid.

Keywords: Enantioselective; Hydrogenation; Chiral modifier; (*S*)-Proline; Enantiomeric excess

1. Introduction

The enantioselective hydrogenation of the prochiral substrates with heterogeneous catalysts is an advantageous way of preparing optically active compounds. In these reactions a chiral modifier is added to the reaction mixture, which creates enantiodifferentiation. In the last two decades intensive research work has been made to discover new enantioselective heterogeneous catalytic systems beside the known two, which are the hydrogenation of ethyl pyruvate to ethyl lactate on platinum catalysts modified with cinchona alkaloids [1] and the enantioselective hydrogenation of β-keto esters on nickel catalysts modified with tartaric acid [2], in both cases the optical purity is above 95%.

Cinchona alkaloids were used as chiral modifiers in the enantioselective hydrogenation of (*E*)-α-phenylcinnamic acid (e.e.∼72%) [3], trifluoroacetophenone (e.e.∼56%) [4], 2-methyl-2-pentenoic acid (e.e.∼50%) [5], etc. A vinca type alkaloid, the (−)-dihydroapovincaminic acid ethyl ester ((−)-DHVIN) was found to be effective modifier in the hydrogenation of the C=C bond of isophorone (e.e.∼55%) [6] and C=O bond of ethyl pyruvate (e.e.∼20%) [7]. The requirements for an effective modifier are the presence of two functional parts: the one anchors it on the catalyst surface, the other interacts with the substrate. For the prochiral substrate to be hydrogenated enantioselectively, these properties are an interactive function with the modifier and a reactive unsaturation [8]. In both previously mentioned modifiers, (−)-DHVIN and cinchonidine (CD), the basic N atom was found to be responsible for the interaction with the substrate [9,10]. The indole ring of (−)-DHVIN might be the anchoring part [9], while CD is anchored to the catalyst surface via its quinoline ring [10].

Structurally simple chiral aminoalcohol modifiers were synthesised by Baiker and co-workers, which possessed the crucial structural parts mentioned above (aromatic ring and basic nitrogen) and tested them

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in the hydrogenation of ethyl pyruvate [11]. The (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl) ethanol was found to be the most effective (e.e.∼75%).

(*S*)-α,α-Diphenyl-2-pyrrolidinemethanol (DPPM), which reminds of the Seebach ligand and was synthesised in our laboratory, afforded 42% optical purity in the hydrogenation of isophorone. However the modifiers from the chiral pool afforded better enantioselectivities than these synthesised molecules.

Our aim was to synthesise chiral compounds possessing easily accessible chiral structural part with basic N atom and condensed aromatic moiety, like indolyl or naphthyl groups. The chiral molecule was the (*S*)-proline, because it is proved to be a good chiral auxiliary in several reactions, among others in the asymmetric heterogeneous catalytic hydrogenation of isophorone, where the chiral auxiliary was added in stoichiometric amount to the solution of the reactant. The hydrogenations of isophorone over Pd-on-carbon catalyst in presence of (*S*)-proline gave high enantiomeric excess (up to 60 %). The hydrogenation reaction itself proved to be diastereoselective as an oxazolidine type intermediate was formed in condensation reaction between isophorone and (*S*)-proline [12].

The hydrogenation of ethyl pyruvate in the presence of (*S*)-proline resulted in the formation of *N*-alkylated proline. Ethyl lactate could not be isolated from the reaction mixture. In a series of experiments (*S*)-proline methyl ester and (*S*)-proline ethyl ester was used instead of (*S*)-proline in 10 mol.% with respect to the ethyl pyruvate and it could be hydrogenated to *R*-(+)-ethyl lactate in low optical purity (1–5% e.e.) [13].

It was supposed that the esterification or amide formation of the (*S*)-proline with condensed aromatic ring containing molecules could result effective chiral modifiers in the asymmetric heterogeneous hydrogenation of isophorone and ethyl pyruvate.

Z-(*S*)-proline 2-naphthyl ester (**1**); *Z*-(*S*)-proline 2-(2-naphthyl)-ethyl ester (**2**); the *Z*-(*S*)-proline 3-ethyl-indole ester (**3**) and the *Z*-(*S*)-proline-3-ethyl-indolamide (**4**) (Scheme 1) were synthesised. (*S*)-proline-2-naphthylamide hydrochloride was also used (**5**, Scheme 2), which was commercially available. All these compounds were tested in the hydrogenation of isophorone and ethyl pyruvate.

2. Experimental

2.1. Materials

The reagents: *Z*-(*S*)-proline (99%), 2-naphthol (99%), 3-(2-aminoethyl)indole (tryptamine, 99%), benzenesulfonyl chloride (99%) and 4-dimethylaminopyridine (DMAP, 99%) were supplied by Fluka, whilst *N*,*N*′-dicyclohexilcarbodiimide (DCC, 99%), 3-(2-hydroxyethyl)-indole (tryptophol, 97%), 2-(2-naphthyl)-ethanol (98%) and pyridine (99%) were purchased from Aldrich.

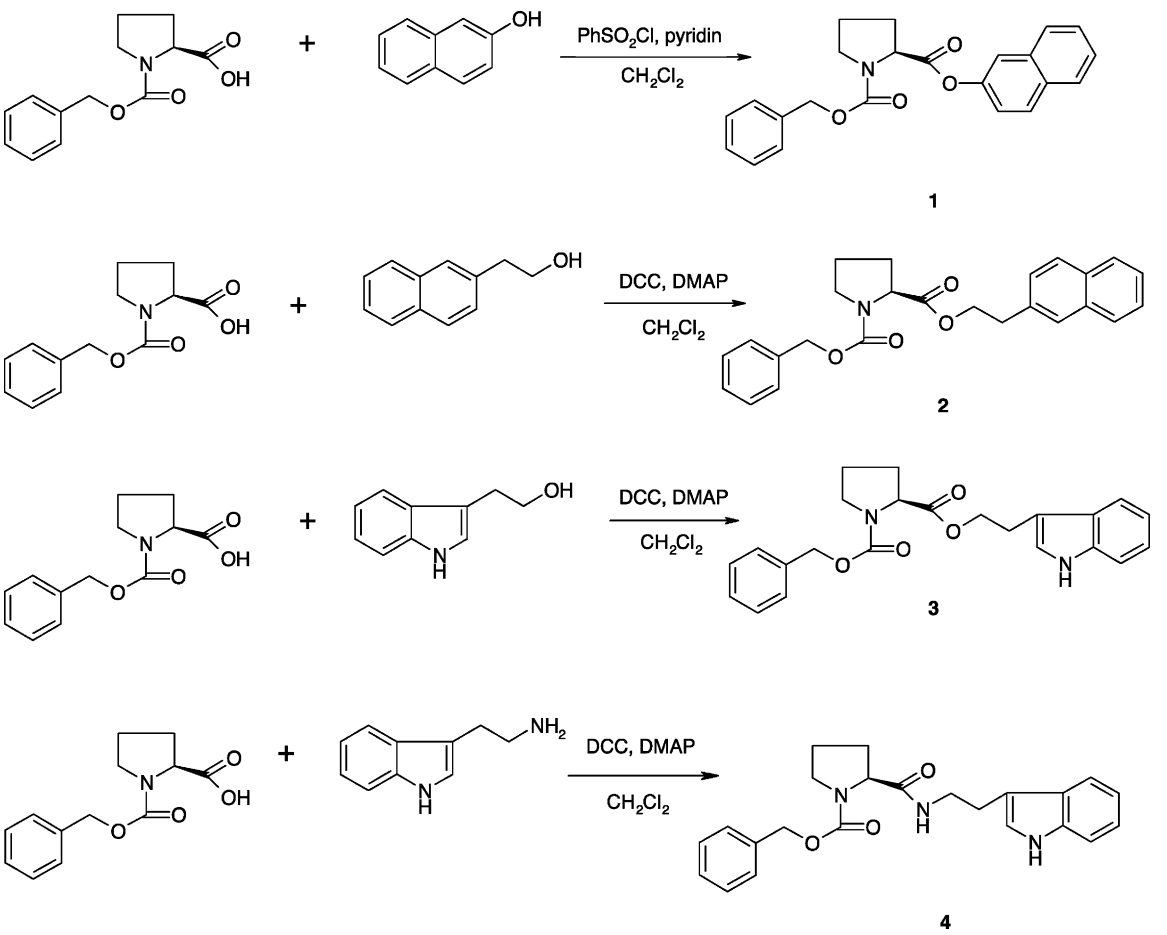
The solvents: methanol, *N*,*N*′-dimethylformamide, dichloromethane, toluene, ethyl acetate were supplied by Reanal in pro analysis grade.

The substrates for hydrogenation: isophorone was supplied by Merck, ethyl pyruvate by Fluka. They were distilled in vacuum before use.

The 5% Pt/Al_2O_3 catalyst was commercial product (JMC). Before use we heat-treated it in a glass reactor for 3 h at 400 °C in a hydrogen stream, then it was cooled down in nitrogen to room temperature. The Pd black catalyst 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. During preparation, the pH of the solution was basic and the whole amount of the reducing agent (HCOONa) was added at the beginning of the reaction.

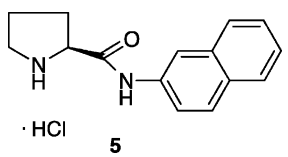
The chiral compounds, such as (**1**) *Z*-(*S*)-proline 2-naphthyl ester, (**2**) *Z*-(*S*)-proline 2-(2-naphthyl)-ethyl ester, (**3**) *Z*-(*S*)-proline 3-ethyl-indole ester and (**4**) *Z*-(*S*)-proline-3-ethyl-indolamide were synthesised (Scheme 1) as described below and (*S*)-proline-2-naphthylamide hydrochloride (**5**, Scheme 2) was supplied by Fluka (99%).

Synthesis of compound (**1**): it was prepared similarly to the procedure described in [14]. To the stirred solution of 0.5 g (2 mmol) *Z*-(*S*)-proline in 2 ml anhydrous pyridine was added 2 ml of freshly prepared 1N solution of benzenesulfonyl chloride in toluene at 0 °C. The mixture was stirred for 15 min followed by the addition of 0.3 g (2 mmol) 2-naphthol. The reaction mixture was heated to room temperature and stirred for 20 h. After adding 10 ml of ethyl acetate the reaction mixture was washed sequentially with 1N HCl, 2% aqueous $NaHCO_3$ and water, dried (sodium sulfate) and concentrated in vacuum to give a crude product.



Scheme 1. Synthesis of chiral modifiers.

Crystallization of the crude material from ethanol gave 0.15 g (20%) of the product (**1**) as a white crystal substance. mp 105 °C, $[\alpha]_D^{20} = -88.2^\circ$ (c = 1, MeOH), ^{1}H NMR: δ ($CDCl_3$) 2–2.4 (m, 4H), 3.5–3.7 (m, 2H), 4.6–4.7 (m, 1H), 5.1–5.3 (m, 2H), 6.9 (d, 1H, Ar-H), 7.1-7.5 (m, 8H, Ar-H), 7.7–7.8 (m, 3H, Ar-H), ^{13}C NMR: δ ($CDCl_3$) 24.1 and 24.9 (CH_2), 30.4 and 31.5 (CH_2), 46.9 and 47.5 (CH_2), 59.4 and 59.9 (CH), 67.5 and 67.7 (CH_2), 118.6 and 118.8 (Ar-CH), 121.1 and 121.3 (Ar-CH), 126.1 and 126.1 (Ar-CH), 126.9 and 127.0 (Ar-CH), 128.0 and 128.1 (Ar-CH), 128.2 and 128.4 (Ar-CH), 128.5 and 128.9 (Ar-CH), 128.9 and 128.131.8 and 131.9 (Ar-C), 134.0 and 134.1 (Ar-C), 136.8 and 137.1 (Ar-C), 148.4 and 148.7 (Ar-C), 154.7 and 155.0 (CON), 171.8 and 171.9 (COO).



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Scheme 2. (*S*)-proline-2-naphthylamide hydrochloride.

Synthesis of compound (**2**): to the stirred solution of 0.93 g (2.2 mmol) *N*,*N*′-dicyclohexylcarbodiimide in 10 ml dichloromethane was added 0.025 g (0.2 mmol) 4-dimethylaminopyridine and 0.54 g (2.2 mmol) *Z*-(*S*)-proline at ambient temperature. The mixture was stirred for 1 h, treated dropwise with the 5 ml solution of 0.34 g 2-(2-naphthyl)-ethanol in dichloromethane

and stirred for 69 h. The afforded *N,N′*-dicyclohexylurea was filtered off. The filtrate was washed sequentially with 1 N HCl, 2% aqueous $NaHCO_3$ and water, dried (sodium sulfate) and concentrated in vacuum to give a residue. The residue was dispersed in *n*-hexane to give 0.3 g (37.5%) of the product (**2**) as a white crystal substance. mp 85 °C, $[\alpha]_D^{20} = -49.5°$ ($c = 1$, MeOH), ^{1}H NMR: δ ($CDCl_3$) 1.8–2.2 (m, 6H), 2.9–3.1 (m, 2H), 3.4–3.6 (m, 2H), 4.3–4.5 (m, 1H), 5.0–5.2 (m, 2H), 7.2–7.3 (m, 7H, Ar-H), 7.3–7.4 (m, 3H, Ar-H), 7.7–7.8 (m, 2H, Ar-H), ^{13}C NMR: δ ($CDCl_3$) 23.4 and 24.2 (CH_2), 29.9 and 30.9 (CH_2), 35.0 and 35.2 (CH_2), 46.4 and 46.9 (CH_2), 58.9 and 59.3 (CH), 65.2 and 65.2 (CH_2), 66.9 and 67.0 (CH_2), 125.5 and 125.6 (Ar-CH), 126.1 and 127.2 (Ar-CH), 127.3 and 127.3 (Ar-CH), 127.4 and 127.5 (Ar-CH), 127.6 and 127.9 (Ar-CH), 128.0 and 128.1 (Ar-CH), 128.2 and 128.4 (Ar-CH), 128.4 and 128.5 (Ar-CH), 132.3 and 132.3 (Ar-C), 133.5 and 133.6 (Ar-C), 135.0 and 135.2 (Ar-C), 136.6 and 136.7 (Ar-C), 154.3 and 154.4 (CON), 172.7 and 172.8 (COO).

Synthesis of compound (**3**): It was prepared by using the same procedure as for the preparation of (**2**). From 0.32 g (2 mmol) Tryptophol and 0.54 g (2.2 mmol) *Z*-(*S*)-proline, 0.75 g (97%) (**3**) was obtained as brownish viscous material. $[\alpha]_D^{20} = -42.2°$ ($c = 1$, MeOH), ^{1}H NMR: δ ($CDCl_3$) 1.6–1.9 (m, 6H), 2.8–3.0 (m, 2H), 3.4–3.5 (m, 2H), 4.0–4.3 (m, 1H), 4.9–5.1 (m, 2H), 6.8 and 6.95 (s, 1H, Ar-H), 7.0 and 7.1 (t, 2H, Ar-H), 7.2–7.3 (m, 6H, Ar-H), 7.4 and 7.5 (d, 1H, Ar-H), 8.0 (s, broad, NH), ^{13}C NMR: δ ($CDCl_3$) 23.6 and 24.4 (CH_2), 30.0 and 31.1 (CH_2), 34.9 and 35.0 (CH_2), 46.6 and 47.1 (CH_2), 59.2 and 59.5 (CH), 65.1 and 65.3 (CH_2), 67.2 and 67.4 (CH_2), 111.3 and 111.4 (Ar-C), 111.8 and 111.9 (Ar-CH), 118.8 and 118.9 (Ar-CH), 119.5 and 119.6 (Ar-CH), 122.2 and 122.3 (Ar-CH), 122.3 and 122.4 (Ar-CH), 127.5 and 127.6 (Ar-C), 128.0 and 128.0 (Ar-CH), 128.1 and 128.1 (Ar-CH), 128.2 and 128.6 (Ar-CH), 136.3 and 136.4 (Ar-C), 136.8 and 136.9 (Ar-C), 154.5 and 155.1 (CON), 172.8 and 173.0 (COO).

Synthesis of compound (**4**): It was prepared by using the same procedure as for the preparation of compound (**2**) and (**3**). From 0.32 g (2 mmol) tryptamine and 0.54 g (2.2 mmol) *Z*-(*S*)-proline, 0.75 g (97%) (**3**) was obtained as brownish crystal substance. mp 90–95 °C, $[\alpha]_D^{20} = -28.6°$ ($c = 1$, MeOH), ^{1}H NMR: δ ($CDCl_3$) 1.6–2 (m, 6H), 2.8–3.0 (m, 2H), 3.3–3.6 (m, 2H), 4.3–4.4 (m, 1H), 5.0–5.1 (m, 2H), 6.9 and 6.9 (s, 1H, Ar–H), 7.2–7.3 (m, 8H, Ar–H), 7.5 (s, broad, NH), 7.6 and 7.7 (d, 1H, Ar–H), 8.2 (s, broad, NH), ^{13}C NMR: δ ($CDCl_3$) 22.3 and 22.9 (CH_2), 27.8 and 28.9 (CH_2), 30.5 and 31.2 (CH_2), 46.6 and 47.1 (CH_2), 54.1 and 55.3 (CH_2), 61.2 and 62.5 (CH), 67.2 and 67.4 (CH_2), 110.3 and 110.4 (Ar-C), 111.7 and 111.9 (Ar-CH), 118.8 and 118.9 (Ar-CH), 119.7 and 119.8 (Ar-CH), 122.2 and 122.3 (Ar-CH), 122.3 and 122.4 (Ar-CH), 127.5 and 127.6 (Ar-C), 128.0 and 128.0 (Ar-CH), 128.1 and 128.1 (Ar-CH), 128.2 and 128.6 (Ar-CH), 136.3 and 136.4 (Ar-C), 136.8 and 136.9 (Ar-C), 154.5 and 155.1 (CON), 168.8 and 169.0 (COO).

The (2*S*)-2(diphenylmethyl)pyrrolidine (DPMP) was prepared according to the procedure described in [17].

2.2. Hydrogenation

The hydrogenation of isophorone and ethyl pyruvate 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. The pH of the reaction mixtures containing modifier (**5**) was adjusted to 8 by addition of triethylamine.

2.3. Analysis

The NMR spectra were recorded on a Bruker DRX500 spectrometer, in $CDCl_3$. Optical rotation was measured with a Perkin-Elmer 241 automatic polarimeter ($c = 1$, MeOH). The reaction mixtures were analysed with a gas chromatograph equipped with a Supelco BETA DEX™ 120 Capillary Column (analysis temperature: dihydroisophorone at 110 °C, ethyl lactate at 90 °C) and FID. The chromatograms were recorded and peak areas were calculated with Chromatography Station for Windows CSW32® v.1.2 (DataApex Ltd. 2001, Prague). 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 $[B]$ is the concentration of minor enantiomer.

3. Results and discussion

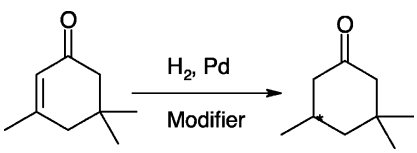
3.1. Catalytic tests

Z-groups of (**1**), (**2**), (**3**) and (**4**) are easily hydrogenolysable under the condition of the asymmetric hydrogenations. It is a necessary step in these reactions, because the substrate establishes an interaction with the modifier through its basic N atom. In the case of the (*S*)-proline-2-naphthylamide hydrochloride the N atom is unblocked after the addition of triethylamine.

In the presence of (**1**), (**2**), (**3**), (**4**), (**5**) the hydrogenation of C=C bond of isophorone (Scheme 3) results in an excess of the (*S*)-(+)-dihydroisophorone.

In Table 1 there are results obtained with (*S*)-proline ester chiral modifiers (0.5 mol.% with respect to the substrate) over Pd black catalyst in different solvents and solvent mixture. The apolar solvents, like toluene, are disadvantageous in this type of reactions (e.e.∼2%).

The greatest asymmetric effect was perceived in methanol. The spacer between the anchoring group and the chiral entity was advantageous for optical purity. (**2**) and (**3**) were considerably more effective than the modifier having no spacing group between the naphthyl ring and the proline. The fixed structure of the compound (**1**) could be the explanation for this phenomenon. The modifier with indole ring (**3**) provided slightly lower optical purity in methanol by about 3% than the modifier with naphthyl ring (**3**), but the difference is not significant.



Scheme 3. Hydrogenation of isophorone.

Table 1
Enantioselectivity for the hydrogenation of isophorone using (*S*)-proline esters as chiral modifiers

Modifier	Conjugated group to (*S*)-proline	e.e. (%)		
		MeOH	MeOH–water 1:1	DMF
1	2-Naphthyl	4	2	5
2	2-Ethyl-naphthyl	23	15	6
3	3-Ethyl-indole	20	1	10

Reaction conditions: 0.01 mol isophorone, 0.05 mmol modifier, 0.05 g Pd black, 10 ml solvent, $p = 50$ bar, $T = 25\,^{\circ}$C, Reaction time 4 h, conversion 100%.

Table 2
Enantioselectivity for the hydrogenation of isophorone using (*S*)-proline amides as chiral modifiers

Modifier	Conjugated group to (*S*)-proline	e.e. (%)		
		MeOH	MeOH–water 1:1	DMF
5	2-Naphthyl	5	7	9
4	3-Ethyl-indole	17	16	19

Reaction conditions: 0.01 mol isophorone, 0.05 mmol modifier, 0.05 g Pd black, 10 ml solvent, $p = 50$ bar, $T = 25\,^{\circ}$C, Reaction time 4 h, conversion 100%.

The enantioselectivities observed using (*S*)-proline amide chiral auxiliaries are listed in Table 2.

For the (*S*)-proline amide chiral modifiers the solvent played a less significant role than in the case of the esters. We found only a little difference in the enantioselectivities regarding the solvent used. While esters induce only a small optical purity in *N*,*N*′-dimethylformamide (DMF), the amide was slightly more effective. It is interesting to notice that the *N*,*N*′-dimethylformamide gave better results both with amides and esters possessing indole ring.

Similarly to the esters, the ethyl group dividing the chiral moiety and the condensed aromatic ring had a beneficial effect on optical purity. This certifies our previous assumption that the modifier having the condensed aromatic ring attached directly to the proline is not mobile enough for inducing higher enantioselectivity.

The efficiency of the modifiers was tested by increasing and decreasing their amount (**2** and **5**) in the reaction mixture. The effect of the concentration on the e.e. is depicted in Fig. 1.

The hydrogenation reaction with compound (**2**) was carried out in methanol, with compound (**3**) in *N*,*N*′-dimethylformamide solvent. In the presence of the modifiers the enantioselectivity reached a limit when the chiral modifier was present in the reaction mixture in 0.5 mol.% with respect to the substrate. Increasing the modifier concentration above this value had no influence on the optical purity. This tendency appears very often in these types of reactions. For

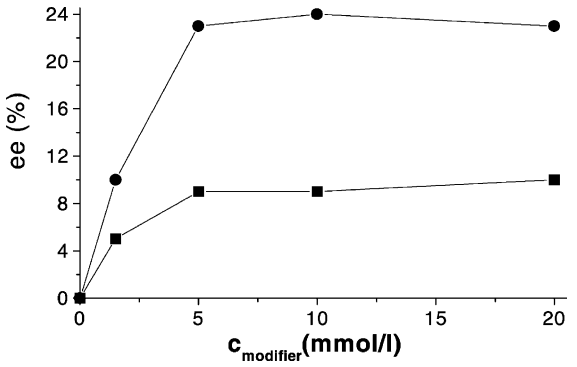
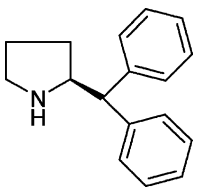


Fig. 1. Enantioselectivity as a function of compound **5** (■) and compound **2** (●) concentrations. Reaction conditions: 0.01 mol isophorone, 0.05 g Pd black, 10 ml MeOH (■), 10 ml DMF (●), $p = 50$ bar, $T = 25\,^{\circ}C$, reaction time 4 h.

comparison, in the same catalytic reaction the optimal value of the (−)-DHVIN/isophorone ratio were 0.3 mol.% [9], and in the case of Pd catalysed enantioselective hydrogenation of α- and β-substituted cinnamic acid derivatives CD/reactant ratio was 3 mol.% [3,15].

It is known that acetic acid affected the enantiomeric excess in positive way in Pd/(−)-dihydroapovincaminic acid ethyl ester mediated reaction. In this case the presence of an acid leads to slight decrease of optical purity (∼4%).

These compounds are very similar in their structure to the previously used (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (DPPM) [16]. However, the DPPM resulted in much higher optical purity (42%), than these novels synthesised chiral compounds. The explanation could be the free hydroxyl group on the DPPM molecule, which probably helps the interaction with the substrate. In order to confirm our assumption, we synthesised the (2*S*)-2(diphenylmethyl)pyrrolidine (DPMP) (Scheme 4) and tested it in the same catalytic reaction. The obtained results are listed in the Table 3.

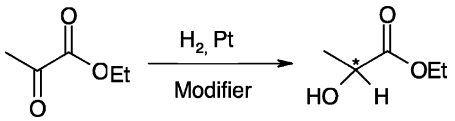


Scheme 4. The (2*S*)-2(diphenylmethyl)pyrrolidine.

Table 3
Enantioselectivity for the hydrogenation of isophorone using the (2*S*)-2(diphenylmethyl)pyrrolidine as chiral modifier

Solvent	e.e. (%)
MeOH	11.5
MeOH–water 1:1	7.5
DMF	18

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, conversion 100%.



Scheme 5. Hydrogenation of ethyl pyruvate.

This chiral compound gave similar results as the (*S*)-proline esters and amides. As the only difference between the structure of DPPM and DPMP is the hydroxyl group, the absence of this group should be responsible for lower e.e. The hydroxyl group plays a crucial role with the basic N atom in the enantiodifferentiation forming a double interaction with the substrate. The interaction between the modifier and the substrate was detected with the circular dichroism spectroscopy [16].

The (*S*)-proline esters and amides were also tested as chiral modifiers in the hydrogenation of C=O bond of ethyl pyruvate (Scheme 5). These chiral molecules afforded an excess of (*R*)-(+)-ethyl lactate (Table 4).

These chiral compounds induced similarly low optical purity in the hydrogenation of ethyl pyruvate as

Table 4
Enantioselectivity for the hydrogenation of ethyl pyruvate using (*S*)-proline esters and amides as chiral modifiers

Modifier	Conjugated group to (*S*)-proline	e.e. (%)	
		AcOH	EtOH
1	2-Naphthyl	0	0
2	2-Ethyl-naphthyl	1	1
3	3-Ethyl-indole	1	0
5	2-Naphthyl	4	3
4	3-Ethyl-indole	5	2

Reaction conditions: 0.01 mol ethyl pyruvate, 0.05 mmol modifier, 10 ml solvent, 0.05 g 5% Pt/Al_2O_3 JMC tt, $p = 50$ bar, $T = 25\,^{\circ}C$, Reaction time 4 h, conversion 100%.

well the (*S*)-proline [13]. Detectable optical purity was obtained with (*S*)-proline amides (∼5%) in acetic acid, on the other hand the (*S*)-proline esters were not effective at all.

4. Conclusions

The planned and synthesised chiral molecules induced an e.e. in the hydrogenation of isophorone and ethyl pyruvate. The assumption is that the basic, secondary N atom in the (*S*)-proline structural part of the modifier interacts with the reactant's carbonyl and the aromatic ring provides the anchoring effect on the metal surface.

In the hydrogenation of ethyl pyruvate the e.e. values were low, corresponding to our expectations, that the (*S*)-proline as additive in the same reaction gave low optical purity too. In the case of isophorone the results were better (e.e.∼23%), however this value is much less than with (*S*)-α,α-diphenil-2-pyrrolidine-methanol (DPPM) (e.e. 42%). Comparing the structure of these compounds, the latter one has also a hydroxyl group, which besides N, probably helps the interaction with the substrate.

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