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New substrates and modifiers in the enantioselective heterogeneous catalytic hydrogenation of the C=C double bond

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Abstract

The Pd catalysed enantioselective hydrogenation of activated C=C bond containing compounds, unsaturated ketones, pyrones and carboxylic acids is discussed, focusing on new substrates, chiral modifiers and their mode of action.

Keywords: Enantioselective; Heterogeneous catalytic hydrogenation; Pd catalysts; Unsaturated ketones; Pyrones; Unsaturated carboxylic acids

1. Introduction

The hydrogenation of β-ketoesters with tartaric acid modified Ni [1] and the hydrogenation of α-ketoesters with cinchona alkaloids modified Pt [2] are the best-known heterogeneous chiral catalytic reactions. In the last two decades several efforts have been made to broad the scope of heterogeneous enantioselective hydrogenations. As result of these studies, new chiral modifiers [3–9] were identified and new prochiral substrates [8–14] have been used with promising enantiomeric excesses. In some of these reactions, Pd appeared as the catalytically active metal. The first Pd catalysed asymmetric hydrogenation of a C=C bond (not considering the early (1950–1956), not reproducible experiments with Pd on silk fibroin and on optically active quartz [15,16]) with significant e.e. was the reduction of isophorone in the presence of (*S*)-proline [17,18].

(*S*)-proline proved to be an excellent homogeneous chiral catalyst in some reactions, for example the Robinson-type condensation of exocyclic α,β-unsaturated ketones. It was suggested that this ability could also be used in heterogeneous hydrogenation. The hydrogenation of isophorone with Pd/C catalyst, in the presence of stoichiometric (*S*)-proline, in methanol as solvent at room temperature resulted in dihydroisophorone with enantiomeric excesses up to 80%. After the uptake of one mol of hydrogen the chemical yield of dihydroisophorone decreased significantly and the major product was the alkylated proline (Scheme 1).

Recently, (*S*)-proline was used also as a chiral auxiliary in the hydrogenation of exocyclic α,β-unsaturated ketones with palladium on carbon catalysts [19], producing the corresponding saturated ketones with an optical purity up to 20% (Scheme 2).

In the case of the exocyclic α,β-unsaturated ketones the zwitterionic form of proline gave the addition and/or condensation product probably in lower concentration, therefore chemo- and enantioselectivity was low (<10%). In order to increase the reactivity of the (*S*)-proline, sodium methylate (NaOMe) was added to convert the proline into its sodium salt, in the presence of the strong base the reduction became chemoselective and gave the saturated ketone in higher optical purity.

The efficiency of (*S*)-proline chiral auxiliary in the above hydrogenations, both in that of the endo- and exocyclic unsaturated ketones, was limited: the e.e. was low or if it was significant then the chemical yield of the saturated ketone became low because of the reductive alkylation of the (*S*)-proline. In these reactions the hydrogenation step was really diastereoselective on the asymmetric route, as the reduction of the chiral and simultaneously prochiral condensation intermediates afforded the optically active saturated ketones (after hydrolysis).

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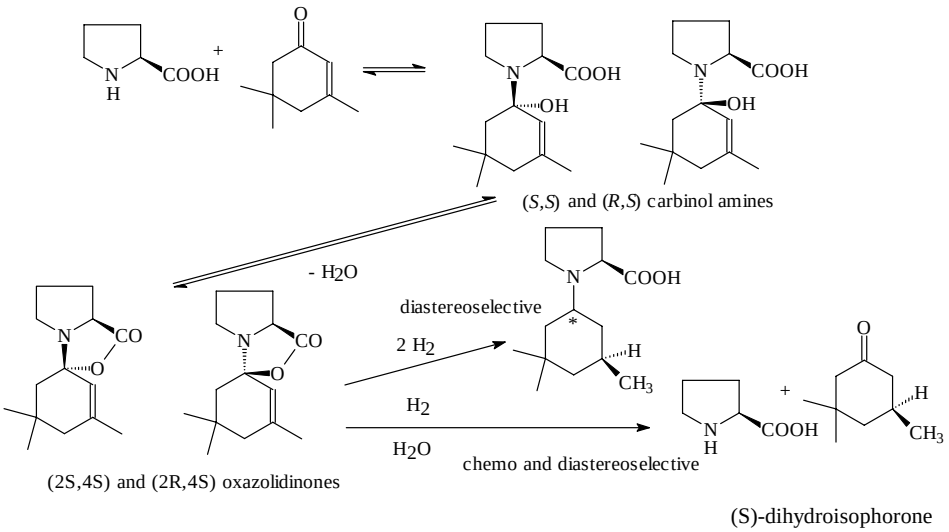


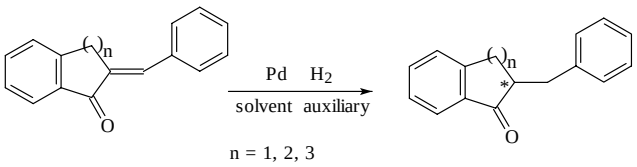
Scheme 1. The reaction pathways in the asymmetric hydrogenation of isophorone with (*S*)-proline chiral auxiliary.

More successful were the chirally modified Pd catalysts used in the hydrogenation of olefins possessing an electron-rich or acidic functional group (Scheme 3) [20–26].

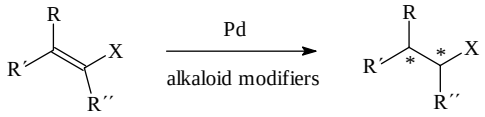
The best modifiers are natural or synthetic alkaloids (Scheme 4).

Efficient modification of Pd requires markedly higher modifier/substrate ratio than that of for Pt. The necessary high modifier concentration leads to significant rate deceleration compared to the racemic reaction carried out in the absence of the modifier.

A brief overview will be given on the achievements with chirally modified Pd catalysts. Special emphasis is placed upon new substrates and new synthesized modifiers. However, an excellent review was published during the preparation of this manuscript [27] and some books [28–30] are also engaged in this topic, the justification of this approach remains. The importance of the heterogeneous catalytic asymmetric reactions, within this that of the hydrogenations is recognised by more and more researchers who are involved in asymmetric synthesis.



Scheme 2. The asymmetric catalytic hydrogenation of (*E*)-2-benzylidene-1-indanone, (*E*)-2-benzylidene-1-tetralone and (*E*)-2-benzylidene-1-benzosuberone.

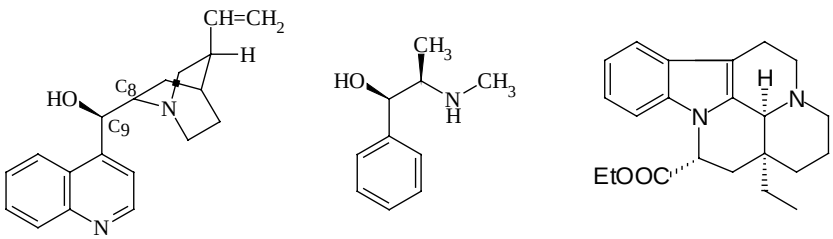


Scheme 3. Enantioselective hydrogenation with modified Pd catalyst. (*R*, *R*′, *R*′′: alkyl, aryl and H; X: electron-rich or acidic functional group).

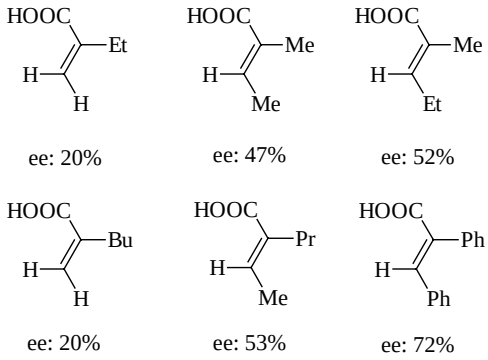
2. Suitable substrates

2.1. α,β-Unsaturated carboxylic acids

The enantioselective hydrogenation of α,β-unsaturated carboxylic acids is widely studied, because the products of those processes are important intermediates in the synthesis of anti-inflammatory agents, such as naproxen and ibuprofen [31–33]. Rhodium and ruthenium complexes were developed for the homogeneous phase hydrogenations producing the saturated acids in excellent enantioselectivity



Scheme 4. Effective modifiers in Pd mediated enantioselective hydrogenations.



Scheme 5. Structural effects in the enantioselective hydrogenation of α,β-unsaturated carboxylic acids over cinchonidine modified Pd [34].

(e.e. ∼ 99%) [33,34]. However, the solid catalysts would be more beneficial due to their technological and economical advantages. The cinchonidine modified supported Pd is a useful solid catalyst in the enantioselective hydrogenation of α,β-unsaturated carboxylic acids [24]. The enantioselectivity strongly depends on the structure of the acid (Scheme 5) [35–37].

According to Baiker and coworkers the feasible explanation for the differences is the double bond migration in the substrate [39]. The cinchona-modified Pd affords good enantioselectivity only if isomerization is slow (internal double bond in the substrate), or this competing reaction is not possible at all (diphenyl substituted alkenoic acid).

Using different cinchonidine derivatives, it was realized that the substrate–modifier interaction involves both the quinuclidine N and the OH group of cinchonidine [40,41]. Methylating the N or removing the OH of the modifier resulted in the complete loss of optical purity. Using hydrogen-chloride or hydrogen-bromide salts of cinchonidine, the e.e. decreased because of the poisonous effect of the halogen, rather than because of the strong protonation of the N.

Baiker and coworkers have developed an empirical model, which could predict the configuration of major product in the hydrogenation of aliphatic alkenoic acid, including indene-carboxylic acids (Scheme 6A) [38].

The *trans*-acid dimer and the aromatic ring system adsorb parallel to the Pd surface, while one of the C=C bonds points towards the quinoline moiety. The acid dimer interacts with cinchonidine via two H-bonds. The major enantiomer is formed by the *syn* addition of two hydrogen atoms from the Pd surface. Spectroscopic analysis and ab initio calculations confirmed the feasibility of the model [35,41]. FTIR studies also confirmed that cinchonidine is able to form cyclic 1:2 complexes with carboxylic acid [42]. Both interactions through the OH and the quinuclidine N of the alkaloid appear to be important factors for the complex formation shown by IR spectroscopy.

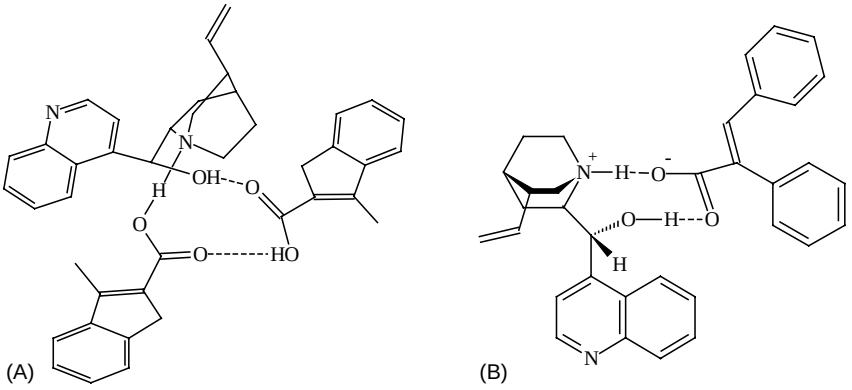
In the enantioselective hydrogenation of (*E*)-α-phenyl-cinnamic acid according to the empirical model of Nitta and coworkers [40] (Scheme 6B) the adsorbed cinchonidine forms two hydrogen bonds with the substrate. Substituting the OH on C9 of the cinchonidine for OCH_3, the enantioselectivity decreased considerably (61%, 18%), while alkylating the N of quinuclidine, the e.e. did not change. The esterification of the carboxyl group of (*E*)-α-phenyl-cinnamic acid damaged the optical purity.

In the enantioselective hydrogenation of (*E*)-α-phenyl-cinnamic acid the best optical purity (72%) was achieved in dimethyl formamide/water 9:1 solvent mixture over Pd/TiO_2 [43,44]. It was a general experience, that the enantioselectivity and the reaction rate considerably increased by adding a small amount of water to aprotic solvents [41,43–45]. It is supposed that the rate determining step for the selective reaction on modified sites is the product desorption step, in contrast to the nonselective reaction on unmodified sites [46]. A small amount of water accelerates this desorption step due to acid–base interaction.

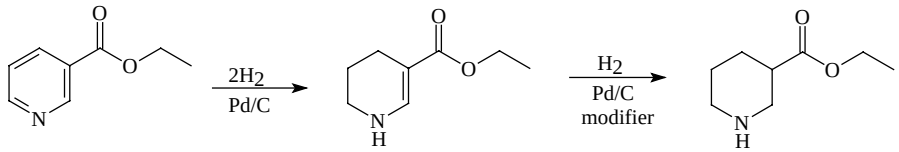
2.2. Ethyl nicotinate

Another example for use of cinchonidine-modified Pd is the preparation of ethyl nipecotinate from ethyl nicotinate in a two step procedure (Scheme 7) [45].

The first hydrogenation step with the uptake of two mol hydrogen was relatively fast, however the hydrogenation of the highly stabilized C=C bond in ethyl



Scheme 6. Supposed cinchonidine–alkenoic acid interactions in the Pd-catalyzed enantioselective hydrogenation.



Scheme 7. Two-step hydrogenation of ethyl nicotinate.

1,4,5,6-tetrahydro-nicotinate proved to be more difficult. The best e.e. of 24% at 10% conversion was achieved with Pd/TiO_2 and cinchonidine in DMF/H_2O (1/1) with trace of acetic acid. This was the first case with chirally modified heterogeneous catalyst to hydrogenate an α,β-unsaturated ester, or considering the tautomery, that of an imine with significant e.e.

2.3. α,β-Unsaturated exocyclic ketones

Muzart and co-workers used ephedrine as chiral modifier or auxiliary, which provided 19–36% e.e. in the enantioselective hydrogenation of some bicyclic α,β-unsaturated indanone and tetralone derivatives (Scheme 2) [13].

Interestingly both (*E*) and (*Z*)-isomers of the substrate afforded the same major enantiomer, though no geometrical isomerization was observed during reaction. A possible explanation could be the involvement of enol species in the enantio-differentiating step.

These exocyclic α,β-unsaturated ketones can be reduced to the corresponding optically active saturated ketones in the presence of cinchona alkaloids [47] over Pd catalysts. The enantioselectivity is strongly dependent on the solvent and the catalyst. 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.

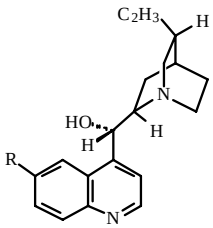
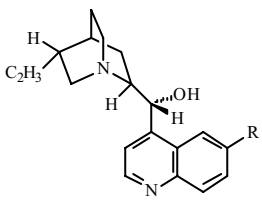
The cinchonidine and quinidine resulted in the *S*, while cinchonine and quinine in the *R* configuration of the saturated ketones. As these modifier pairs are quasi-enantiomers, they afforded different enantioselectivity values (Table 1).

Under the same conditions, the enantioselectivity was much lower for the five-, and six-member ring containing compounds. These significant differences between the enantioselectivity values can be attributed to the different rigidity and associate-forming ability of the substrate molecules [19].

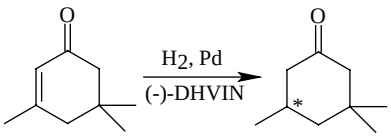
2.4. α,β-Unsaturated endocyclic ketone, isophorone

Another thoroughly investigated reaction over Pd is the hydrogenation of α,β-unsaturated endocyclic ketones. A vinca alkaloid, the (−)-dihydroapovincaminic acid ethyl ester ((−)-DHVIN) was found to be effective modifier in the hydrogenation of the C=C bond of isophorone [8] affording 55% e.e. of the corresponding saturated ketone (Scheme 8). Cinchona alkaloids were moderately effective (∼20% e.e.).

Table 1
Effects of cinchona alkaloid on the enantioselectivity

Modifier		*R*	e.e. (%)	Configuration
Cinchonidine		H	53.7	*S*
Quinine		OCH_3	36.7	*R*
Cinchonine		H	36.5	*R*
Quinidine		OCH_3	51.4	*S*

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



Scheme 8. Enantioselective hydrogenation of isophorone.

With circular dichroism spectroscopic investigations and detailed studies of the reaction the probable processes of enantiodifferentiation could be clarified (Scheme 9). The enantiomeric excess of the product depends in every case on the equilibrium of adduct forming and adsorption reactions and the relative rates of competing hydrogenations, namely that of the chiral and racemic reactions.

It is believed that the (−)-dihydroapovincaminic acid ethyl ester as a chiral modifier interacts through the basic N with the carbonyl group of the substrate. The asymmetric effect is greater if the N is protonated by a week acid, for example acetic acid. Strong acids terminate the interaction, because they form close ion-pairs and the anions exclude the substrate molecules [8,11,48,49].

The substrate–modifier interaction exists, according to CD, in solution, probably in the form of aggregates. They may contain substrate and modifier molecules in sandwich-like form, which probably remain in adsorbed state on the surface of the catalyst too. The aggregates may be similar to those described in enantiomer separation processes [40].

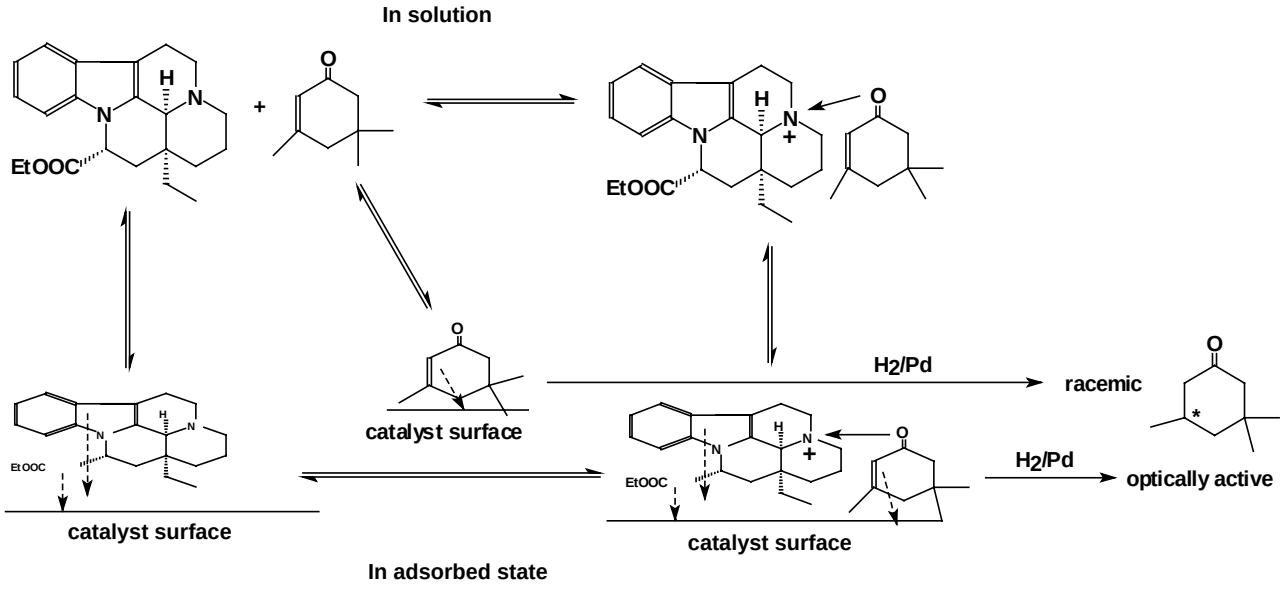
2.5. Substituted 2-pyrones

An important new application of cinchona modified Pd is the enantioselective hydrogenation of 4-alkoxy and 4-methyl derivatives of 2-pyrone [50]. These studies demonstrate that the potential of chirally modified Pd is much broader than has been commonly considered and its efficiency is comparable with those of Pt-cinchona and Ni-tartarate systems [51]. The asymmetric hydrogenation of substituted 2-pyrones has gained increasing interest in pharmaceutical chemistry, due to the importance of the structure of 2-pyrone and its partially hydrogenated derivatives in natural and synthetic biologically active compounds [52,53].

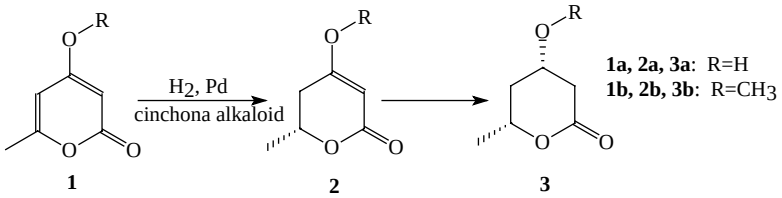
Hydrogenation of pseudo-aromatic compound 4-hydroxy-6-methyl-2-pyrone (1a) (Scheme 10) resulted in (*S*) enantiomer of the corresponding dihydropyrone (2a) with 85% e.e. in acetonitrile [54,55].

The mechanistic model based on catalytic, spectroscopic studies, and on theoretical calculations, is depicted in Scheme 11 [56].

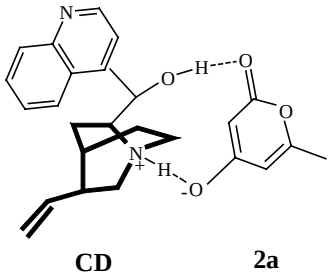
In this bidentate modifier-reactant complex the interaction of the basic quinuclidine N of cinchonidine ($pK_a = 10.0$



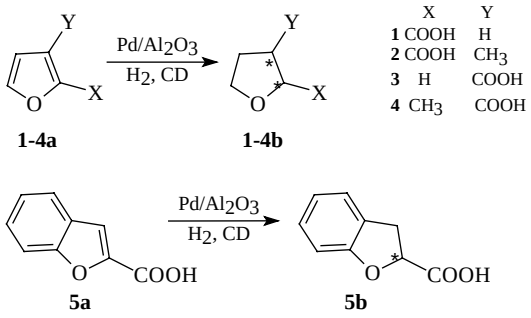
Scheme 9. Possible processes in the enantioselective hydrogenation of isophorone.



Scheme 10. Hydrogenation of 2-pyrone derivatives over cinchona-modified Pd.



Scheme 11. Reactant-modifier interaction responsible for enantiodifferentiation in the hydrogenation of 4-hydroxy-6-methyl-2-pyrone [52].



Scheme 12. Hydrogenation of furan and benzofuran carboxylic acids over 5 wt.% Pd/Al_2O_3 modified by cinchonidine (CD).

[57]) with the acidic OH function of 1a ($pK_a = 4, 73$ [58]) plays a crucial role.

Addition of strong base or acid should therefore hinder the reactant–modifier interaction and diminish the e.e., but even a large excess of TFA did not hinder completely the enantiodifferentiation in acetonitrile, only lowered the e.e. considerably. The real modifier might be a three-membered cyclic complex involving the alkaloid modifier, TFA and the reactant, which is believed to form during reaction.

Further investigation of the application range of the catalyst revealed that some 2-pyrone derivatives can effectively be hydrogenated even in the absence of an acidic functional group. It means that the mechanism discussed above is not valid for the hydrogenation of 4-methoxy-6-methyl-2-pyrone (1b). It have been produced the (*R*) enantiomer of 2b with 94% e.e. and 95% chemoselectivity at 80% conversion over Pd/TiO_2 in the presence of cinchonine [51]. This is the highest enantioselectivity reported for any enantioselective hydrogenation over chiraly modified Pd. A critical point is the low reactant/catalyst or reactant/modifier ratio. 90% e.e. was achieved with 105 1/CN ratio, but a ratio of 2.1 was necessary to improve the e.e. to 94%.

The enantioselective hydrogenation of 4-methoxy-6-methyl-2-pyrone (1b) was conducted in continuous fixed-bed reactor [59]. Good enantioselectivity could be achieved only at very low conversion. The necessary cinchona alkaloid/reactant ratio is remarkably higher in continuous reactor than in batch reactor. Hence, a batch reactor is the best choice for the heterogeneous catalytic synthesis of chiral dihydropyrones.

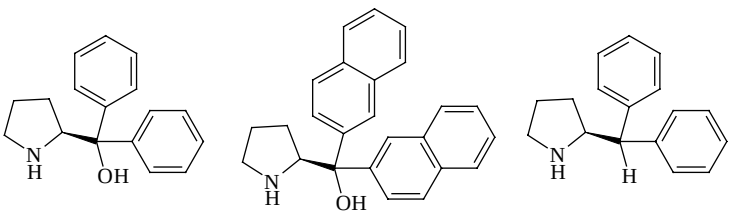
Modulation excitation spectroscopy and phase-sensitive detection in combination with attenuated total reflection (ATR) infrared spectroscopy was applied to study catalytic solid-liquid interfaces of powder catalyst in situ in the enantioselective hydrogenation of 4-methoxy-6-methyl-2-pyrone [60]. Carboxyl and carbonyl species were detected, which strongly compete with cinchonidine even at very low concentration for adsorption sites.

The FTIR, NMR and NOESY-NMR spectroscopic analysis and ab initio calculations revealed that the e.e. is determined by competing reactant-modifier interactions in the enantioselective hydrogenation of 2-pyrone derivatives [61].

2.6. Furan and benzofuran carboxylic acids

Another novel use of cinchona-modified Pd is the asymmetric hydrogenation of furan and benzofuran carboxylic acids (Scheme 12) [62].

This catalyst system is moderately effective. 32% e.e. has been achieved at full conversion of furan-2-carboxylic acid (1a) to its tetrahydro derivative (1b) and 50% e.e. at 29% conversion of benzofuran-2-carboxylic acid (5a) to its dihydro derivative (5b). These e.e. values are the highest obtained so far in the asymmetric hydrogenation of furan derivatives [63]. A major limitation of cinchona modified Pd is the competing hydrogenation of the alkaloid modifier, necessitating low substrate/modifier ratios (6.5–22). The assumption is that the substrate-modifier interaction on the Pd surface resembles that of alkenoic acid hydrogenation over cinchona modified Pd.



Scheme 13. Pyrrolidine-methanol derivatives.

Table 2
Pyrrolidine–methanol derivatives as chiral modifiers in the enantioselective hydrogenation of isophorone

Modifier	Solvent	Conversion (%)	e.e. (%)
DPPM	MeOH–H_2O, 1:1	100	42 [66]
DNPM	DMF	69	25 [65]
DPMP	DMF	100	18 [67]

3. Synthesised chiral modifiers

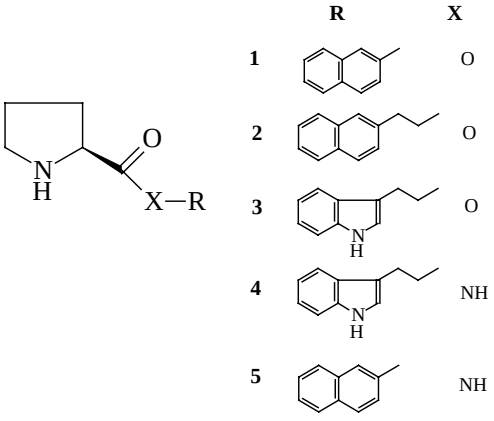
As result of the extensive work with modified reactions it turned out that enantioselectivity is very sensitive to structural changes of the chiral modifier. The requirements for significant enantioselectivity are: two functional parts of the modifier, the one for anchoring on the catalyst surface (usually a condensed aromatic moiety) and the other for interaction with the substrate (preferably a tertiary or secondary N in chiral environment). For the prochiral substrate these requirements are: an interactive function with the modifier (for example a keto-carbonyl group) and a reactive function (C=C) [64]. In both modifiers, in (−)-DHVIN and cinchonidine (CD) the basic N atom was found to be responsible for the interaction with the substrate [11,65]. The indole ring of (−)-DHVIN might be the anchoring part [11], while CD is anchored to the catalyst surface via its quinoline ring [65].

3.1. Pyrrolidine-methanol derivatives

The (*S*)-α,α-diphenil-2-pyrrolidinemethanol (DPPM) (Scheme 12) used in homogeneous catalysed enantioselective reduction of prochiral ketones [66–68] fulfils the requirements described above, therefore it was tested in the hydrogenation of C=C bond of isophorone.

Two kindred compounds, the (*S*)-α,α-dinaphthyl-2-pyrrolidinemethanol (DNPM) and (2*S*)-2(diphenylmethyl) pyrrolidine (DPMP) were also (Scheme 13) studied in the hydrogenation of C=C bond of isophorone (Table 2) [69,70].

It was assumed that the basic, secondary N atom in the pyrrolidine ring of these modifiers was responsible for



Scheme 14. (*S*)-proline based chiral modifiers.

Table 3
(*S*)-proline based chiral modifiers in the enantioselective hydrogenation of isophorone

Modifier	Solvent	e.e. (%)
1	DMF	5
2	MeOH	23
3	MeOH	20
4	DMF	19
5	DMF	9

interaction with the reactant. The interaction of DNPM chiral modifier with the substrate isophorone was detected using circular dichroism spectroscopy. The e.e. differences between the results obtained with DPPM and DPMP could be attributed to the presence and the absence of the hydroxyl group, which probably gives, together with the nitrogen, a bidentate type interaction with the substrate.

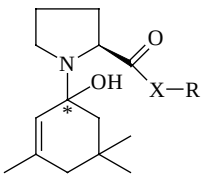
With respect to the aromatic moieties of modifiers it was supposed that DNPM with two naphtyl groups exerted stronger anchoring effect, but it gave lower optical purity. Probably the two naphtyl groups on the same carbon atom make the molecule too bulky, weakens the interaction of the modifier with the catalyst surface.

3.2. (S)-proline based molecules

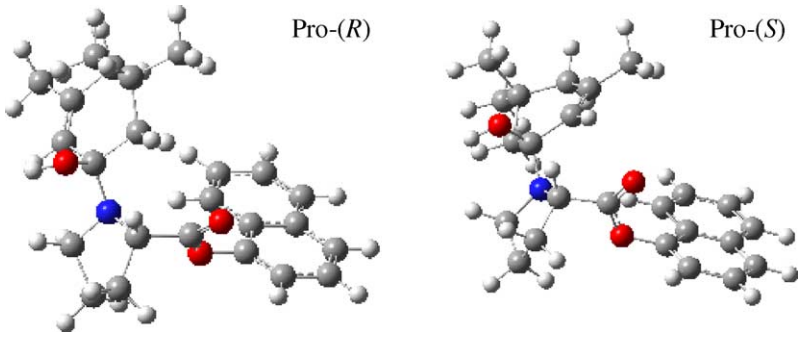
Further examples of synthesized chiral modifiers in the enantioselective hydrogenation of isphorone are (*S*)-proline based molecules also (Scheme 14) [71].

(*S*)-proline esters and amides containing condensed aromatic moiety resulted in excess of *S* enantiomer in the asymmetric heterogeneous hydrogenation of isophorone (Table 3) [71]. The spacer between the anchoring group and the chiral entity was advantageous for optical purity.

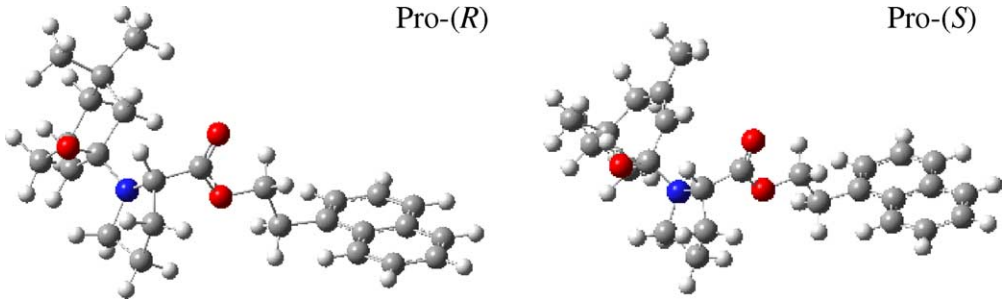
The aim was to synthesize chiral compounds possessing easily accessible chiral structural part with basic N atom and condensed aromatic moiety, like indolyl or naphthyl groups. The chiral molecule was the (*S*)-proline, because it is proved to be a good chiral auxiliary in several reactions, among others in the asymmetric heterogeneous catalytic hydrogenation of isophorone [17]. The hydrogenation of isophorone over Pd-on-carbon catalyst in presence of (*S*)-proline proved to be diastereoselective as an oxazolidinone type intermediate was formed in condensation reaction between isophorone and (*S*)-proline [18]. Based on that reaction it is supposed that (*S*)-proline esters and amides form an adduct in the course of the reaction (Scheme 15).



Scheme 15. Proposal for the type of intermediate between isophorone and (*S*)-proline derivatives.



Scheme 16. Calculated structures of possible adduct formed between isophorone and (*S*)-proline (2-naphthyl) ester (1).



Scheme 17. Calculated structures of possible adduct formed between isophorone and (*S*)-proline [2-(2-naphthyl)-ethyl] ester (2).

Table 4
The energy values of possible adducts formed between isophorone and (*S*)-proline esters and amides

Modifier	Binding energy* (kJ/mol)		ΔE^* (kJ/mol)
	pro-(*S*)	pro-(*R*)	
1	31.45	31.83	−0.38
2	28.05	31.91	−3.86
3	324.28	320.07	4.21
5	34.69	35.05	−0.36
4	36.83	36.85	−1.02

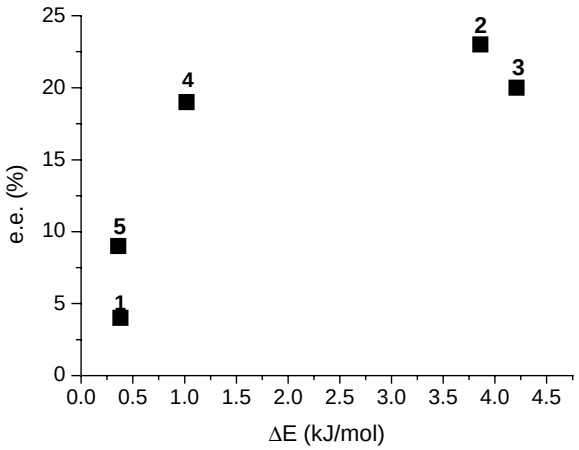


Fig. 1. The correlation between e.e. and ΔE of pro-(*S*) and pro-(*R*) diastereomers.

The structures of possible adducts were fully optimised and the energies were calculated using the HF method with the 6–31*G** basis set (Table 4) with help of Gaussian 98 [72].

Schemes 16 and 17 show structures of possible adducts calculated at the ab initio level.

The theoretical calculations were in agreement with experimental results (Fig. 1), the larger the energy differences between the pro-(*S*) and pro-(*R*) intermediates, the larger were the e.e. values in the hydrogenations.

4. Summary

The developments were summarised in the enantioselective Pd catalysed heterogeneous catalytic hydrogenation of the C=C bond. The substrates were endo- and exocyclic unsaturated ketones, unsaturated carboxylic acids, pyrones and furan carboxylic acids, the chiral modifiers were, beside the cinchona alkaloids, (−)-dihydroapovincaminic acid ethyl ester, ephedrine, diphenylpyrrolidine methanol and esters and amides of (*S*)-proline. Further on cinchonidine induced the best enantioselectivities, however synthetic modifiers, (−)-dihydroapovincaminic acid ethyl ester and diphenylpyrrolidine methanol, the latter lent from homogeneous chiral catalysis, were promising also. The interactions between substrates and modifiers are diverse, they can be acid-base, carbonyl-basic nitrogen type connections, supplemented by hydrogen bridges. The bidentate interactions seem to be more effective. The anchoring parts of the

modifiers are aromatic moieties preferably condensed rings. The modification of Pd requires higher modifier ratio than that of Pt, in some reaction the saturation of the modifier could be detected, which leads to loosing its anchoring capability and the decrease of the e.e.

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