Synthetic Modifiers for Platinum in the Enantioselective Hydrogenation of Ketopantolactone: A Test for the Mechanistic Models of Ketone Hydrogenation

Elisabeth Orglmeister, Tamas Mallat, Alfons Baiker*

Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology, ETH Hönggerberg, 8093 Zürich, Switzerland
Phone: (+41)-1-632-3153, Fax: (+41)-1-632-1163, e-mail: baiker@chem.ethz.ch,

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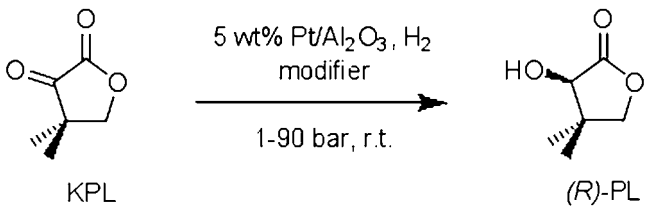
Abstract: Various derivatives of (*R*)-1-(1-naphthyl)-ethylamine have been synthesized and tested as chiral modifiers of Pt/alumina in the enantioselective hydrogenation of ketopantolactone. The best modifiers (ee up to 79%) possess an ester function in the α-position to the amino group. The modifiers performed far better in AcOH than in toluene, indicating that protonation of the N atom is important in enantioselection. The striking non-linear behaviour of modifier mixtures with cinchonine indicates that the alkaloid adsorbs much stronger on Pt than the naphthylethylamine derivatives. Two mechanistic models are proposed for interpretation of the results, involving an N–H–O or N^+–H–O bond between the amine-type modifier and the keto carbonyl O atom of ketopantolactone, in apolar and protic media, respectively. In both cases the H atom originates from the modifier and not from the substrate ("half-hydrogenated-state"). The higher ee achieved in acidic medium is attributed to the better proton donor ability of the protonated amine modifiers. The models are applicable also to the hydrogenation of ethyl pyruvate.

Keywords: asymmetric heterogeneous catalysis; chiral modifier; hydrogenation; ketopantolactone; naphthylethylamine derivatives; platinum/alumina

Introduction

Catalytic hydrogenation of organic compounds containing a carbonyl group is industrially important in the synthesis of fine chemicals and pharmaceuticals. Cinchona alkaloid-modified Pt is an efficient heterogeneous catalyst for the enantioselective hydrogenation of activated ketones.[1–5] Usually the hydrogenation of alkyl pyruvate to alkyl lactate is chosen as a model reaction and has been extensively studied in this context but this industrially unimportant transformation is complicated by numerous side reactions.[1,6,7] From a practical point of view, enantioselective hydrogenation of ketopantolactone (KPL) to (*R*)-pantolactone (PL), an intermediate in the synthesis of vitamin B5 and co-enzyme A, is the most promising application of cinchonidine-modified Pt (Scheme 1). Under optimized conditions cinchonidine (CD) as chiral modifier of Pt/Al_2O_3 affords 91.6% ee in toluene,[8] and a continuous process in a fixed-bed reactor is also feasible.[9] For comparison, several highly selective chiral Rh and Ru complexes have been developed for the hydrogenation of KPL, which afford up to 99% or higher ee under ambient conditions.[10–15] Although heterogeneous catalysis has some obvious advantages and the optical purity of (*R*)-PL can be increased by recrystallization, improvement of the enantioselection on Pt is necessary for practical application.

Supported by theoretical calculations, we proposed a model for the reactant-modifier interaction on the Pt surface involving an H bond between CD and the half-hydrogenated state derived from KPL (Figure 1).[16,17] The model fits well to the catalytic results and spectroscopic observations concerning the adsorption of CD on Pt [18,19] and even the hydrogen-bonding interaction



Scheme 1. Hydrogenation of ketopantolactone (KPL) to (*R*)-pantolactone ((*R*)-PL) over chirally modified Pt/Al_2O_3. The structure of the modifiers is shown in Figure 2.

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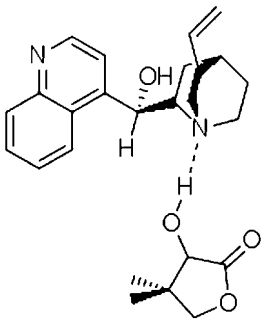


Figure 1. Top view over the Pt surface of a calculated model for interaction of ketopantolactone (half-hydrogenated state) with cinchonidine, leading upon hydrogenation to (*R*)-pantolactone.

has been confirmed recently by *in situ* ATR-IR spectroscopy.[20]

A proven strategy to learn more about the reaction mechanism is the systematic variation of the structure of the modifier. The approach has the inherent advantage that the results are related to truly *in situ* conditions. This strategy has been applied extensively for the hydrogenation of pyruvate esters on Pt, including some cinchona alkaloid derivatives,[21–26] other alkaloids,[27–30] various amines,[31,32] amino alcohols,[33–37] amino acids,[38] and amino acid derivatives.[39,40] The most important conclusions emerging from these studies are that CD and many other effective modifiers adsorb *via* the extended aromatic ring lying close to parallel to the Pt surface, and the basic N-atom is responsible for interacting with the substrate in the enantiodifferentiating step. A somewhat disappointing conclusion from all these studies is that none of the new synthetic modifiers could surpass the performance of CD or its *O*-methyl derivative.

The strategy of varying the modifier structure has recently been extended to the hydrogenation of KPL. Increasing bulkiness of the ether derivatives of CD resulted in the inversion of enantioselectivity to (*S*)-PL.[41] The striking changes highlight the importance of steric effects (repulsive interaction) in enantioselection, beside the above-mentioned attractive interaction (Figure 1). The results provided also indirect evidence for the adsorption of CD *via* the quinoline ring being close to parallel to the Pt surface.

The aim of the present study was to improve our understanding of the modifier-reactant interaction on the Pt surface with emphasis put on the surroundings of the N atom. To circumvent the difficulties of alkaloid chemistry, we synthesized and tested various derivatives of (*R*)-1-(1-naphthyl)ethylamine **1**. It has been shown earlier that **1** and its *N*-alkylated derivatives may be considered as simple and relatively effective analogues of CD in the Pt-catalyzed hydrogenation of ethyl pyruvate.[16,42]

Results and Discussion

Structural Effects

The chiral modifiers synthesized from **1**, and the best enantioselectivities to (*R*)-PL, are shown in Figure 2. More details of the reactions carried out in toluene or acetic acid (HOAc) are summarized in Table 1. The conditions are not optimized although some key parameters have been varied and the highest enantioselectivities for both solvents are presented. The data in Table 1 reveal that most of the modifiers containing an amino function perform significantly better in HOAc than in toluene. The importance of protonation of the modifier in the reaction mechanism will be discussed later.

The primary amine **1** afforded almost five times higher ee to (*R*)-PL in AcOH than in toluene. It has been found earlier that in the hydrogenation of another activated ketone, ethyl pyruvate, the actual chiral modifier of Pt is rapidly produced *in situ* from **1** by reductive alkylation with the substrate.[32] In contrast, no reductive alkylation of **1** occurred during KPL hydrogenation in HOAc or toluene, as evidenced by NMR analysis. Moreover, neither hydrogenolysis of the C–N bond ("benzylic" carbon) nor hydrogenation of the naphthyl ring of **1** could be observed in toluene under the reaction conditions. In HOAc the naphthyl ring was partially saturated. This side reaction was, however, slow compared to the hydrogenation of KPL and did not influence the enantioselectivity as indicated by the constant ee (within $\pm 1\%$) up to full conversion.

The performance of **1** could not be improved by alkylation of the N atom. Increasing the bulkiness around the N atom by methylation (**2, 3**) resulted in a successive loss of enantioselection. The *N*-adamantanyl derivative **6** performed better but the big variation in ee (7–51%) among the monoalkylated derivatives **2** and **4** – **7** cannot easily be interpreted in terms of a conformational concept. Note that in the absence of acid **4** gave the highest ee among all modifiers tested (37%).

Benzylation of **1** (to afford **8**) improved slightly the ee compared to the methylated derivative **2**. When the reaction was repeated in toluene at 30 bar but in the absence of KPL, modifier **8** remained fully intact according to NMR analysis. Modifier **8** was less stable in HOAc (in the absence of substrate) as illustrated in Scheme 2 and Figure 3. Within 2 h, **8** was completely transformed to the *N*-benzyltetrahydronaphthalene-derivatives **8a** and **8b**, and debenzylated to **1a** and **1b**. The debenzylation reaction was much slower than saturation of the aromatic ring and only small amounts of the aromatic debenzylated product, which is identical to modifier **1**, could be found as an intermediate. For comparison, in the enantioselective hydrogenation of KPL in HOAc under the same conditions 50% conversion was achieved within 2–2.5 min. (Note that the time indicated

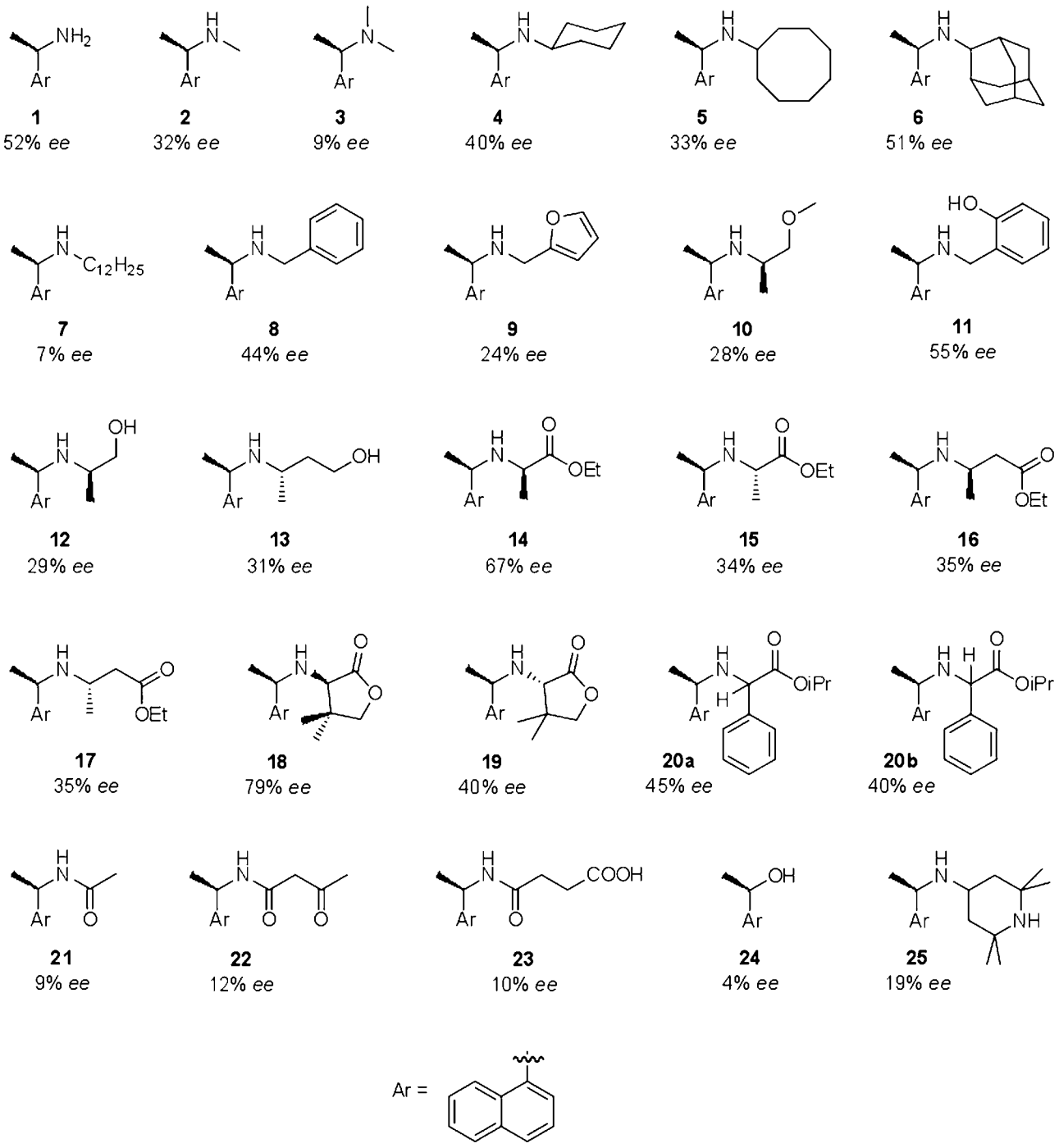


Figure 2. (*R*)-1-(1-Naphthyl)ethylamine **1** and its derivatives, and the best ees they provided as chiral modifiers of Pt/Al_2O_3 in the hydrogenation of KPL.

in Table 1 is usually much longer than the actual reaction time as following the conversion by the hydrogen consumption was inaccurate due to the small reaction scale.) It also has to be considered that hydrogenation of **8** is probably much slower in the presence of the reactive KPL in 270-fold excess. Hence, distortion of the enantioselectivity by transformation of **8** is assumed to be minor.

When modifier **8** was employed as its HCl salt, the ee barely changed in HOAc, whereas in toluene it increased from 16 to 25%. This improvement can be taken as an evidence for the better efficiency of protonated amine modifiers.

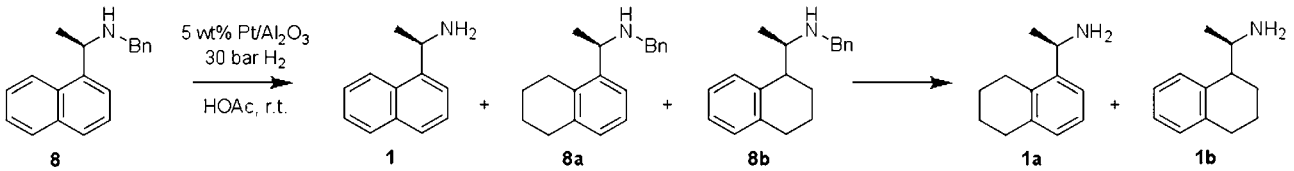
Next, the influence of functionalized side chains attached to the N atom was investigated, assuming that a "double" interaction with the substrate involving both

Table 1. Performance of the modifiers in the enantioselective hydrogenation of KPL to (*R*)-PL. Only the highest values measured at full conversion (except for modifiers **15** and **23**, where conversion in HOAc was 95%) are reported for each modifier. Standard conditions, 5 or 10 mL solvent (no significant influence).

	In Toluene				In HOAc			
Modifier	H_2 [bar]	Catalyst [mg]	Time [h]	ee [%]	H_2 [bar]	Catalyst [mg]	Time [h]	ee [%]
1	70	21	1	11	30	11	0.5	52
2	30	21	1	15	30	21	1	32
3	30	20	0.75	9	10	20	0.75	4[a]
4	70	21	0.5	37	15	10–21	1.75	40
5	90	21	0.5	22	30	21	1	33
6	10–30	20	1.5	9	10	10	1.5	51
6[b]	10	20	1.5	48	–	–	–	–
7	10	20	2.5	7	10	10	2.5	6[a]
8	30	21	1	16	30	21	2	44
8[c]	30–70	21	1	25	30	21	1	43
9	30	20	1	13	10	10–20	2	24
10	30	20	2	9	10	10–20	2	28
11	90	21	0.5	20	10	10.5	0.5	55
12	30	20	2	19	10	10.5	2	29
13	30	20	1	21	10	10.5	2	31
14	90	21	0.5	26	10	10.5	0.5	67
15	30	20	2	7	10	10	0.5	34
16	30	20	2	23	10	20	2	35
17	30	20	2	21	10	20	2	35
17[c]	30	20	0.75	20	10	20	2	26
18	30	5	4	5	10	3	4	74
18[b]	8	5	3	79	–	–	–	–
19	30	10	3	4	10	10	3	40
20a	10	20	2.5	3	20	10	2.5	45
20b	30	20	3.5	3	10	10	3.5	40
21	10	20	2.5	0.5	3	20	2.5	9
22	10	20	0.75	6	10	10	4	12
23	3	10	4	3	3	10	4	10
24	10	20	1.75	4	10	20	1.75	3
25	10	20	1	13	10	20	1	19

[a] The (*S*) enantiomer formed in excess.
[b] Addition of 136 μmol TFA to the toluene solution, reaction performed at 0 °C.
[c] The modifier was used as its HCl salt.

functional groups of the modifier might improve the ee. It has been found recently that a chiral diol (1-naphthyl-1,2-ethanediol) can induce ee up to 30% in the hydrogenation of KPL, presumably due to formation of two H bonds with the keto carbonyl group of KPL.[43] Compounds **9** and **10**, possessing an ether O function in 1,4-position to the N atom, are poor modifiers. Introduction of a phenolic OH function in **11** improved slightly the enantioselectivity compared to **8**. An alcoholic OH function in 1,4- or 1,5-position to the N was less effective (modifiers **12** and **13**, respectively). The possible interaction of a single OH function of the modifier with KPL was tested by replacing the amino group of **1** by an OH group in **24**. The very low ee of 3–4% shows that this approach was not fruitful.



Scheme 2. Hydrogenation of **8** under standard reaction conditions, in HOAc. Under the same conditions but in toluene modifier **8** remains completely intact (see also Figure 3).

Table 2. Influence of solvent polarity (characterized by the empirical solvent parameter E_T^N) on the hydrogenation of KPL to (*R*)-PL over Pt/Al_2O_3 modified by **18**. Standard conditions, 5 mL solvent. Conversions were 98–100%, except in DMF (57%).

Solvent	E_T^N	H_2 [bar]	Catalyst [mg]	Time [h]	ee [%]
$PhCH_3$	0.099	30	5	4	5
THF	0.207	10	20	1.5	10
EtOAc	0.228	10	20	2	8
$PhCF_3$	0.241	30	20	1.5	48
DMF	0.404	3	20	1.5	2
AcCN	0.46	30	20	2	1
i-PrOH	0.546	10	20	2	14
HOAc	0.648	10	3	4	74

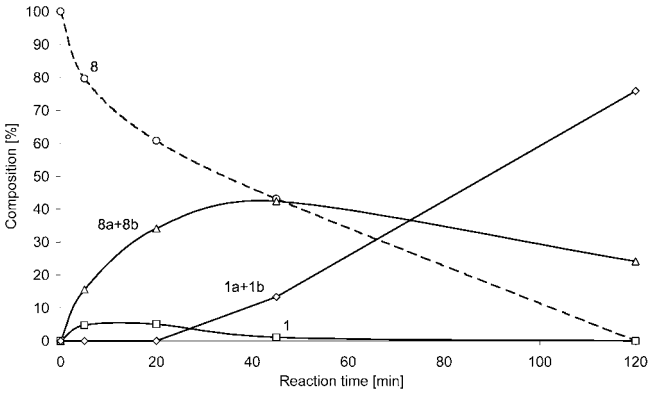


Figure 3. Hydrogenation of **8** in HOAc in the absence of KPL, according to Scheme 2. Conditions: 30 mg catalyst, 5 mL HOAc, 6.8 μmol modifier, room temperature, 30 bar.

Table 3. Influence of chiral modifier on the rate of ketopantolactone (KPL) hydrogenation characterized by the conversion achieved in 15 min and the turnover frequency. Standard conditions, 20 mg catalyst, 10 ml solvent, 1 bar.

Modifier	Solvent	Conversion [%]	TOF[a] [h^{-1}]
no	$PhCH_3$	50.1	1800
18	$PhCH_3$	73.9	2650
cinchonidine	$PhCH_3$	74.2	2660
no	HOAc	25.1	900
18	HOAc	67.3	2420
cinchonidine	HOAc	72.1	2590

[a] TOF = mol KPL converted per h divided by mol Pt atoms on the surface.

The α-amino ester-type modifier **14** provided 67% ee (*R*)-PL in HOAc. The improved enantioselectivity compared to **1** is attributed to the presence of the ester carbonyl group. In contrast to **14**, the other diastereomer **15** is a much weaker modifier. A similar difference in the efficiency of **14** and **15** has been observed in ethyl pyruvate hydrogenation.[44] When the distance between the amino and ester groups was widened by one CH_2 unit in **16**, the ee to (*R*)-PL decreased. In this case, both diastereomers **16** and **17** gave comparable ees, even when **17** was applied as the HCl salt.

Another α-amino ester-type modifier (**18**, **19**) was synthesized from **1** by reductive alkylation with KPL. One of the two diastereomers, **18**, induced 74% ee in the hydrogenation of KPL in HOAc. Interestingly, in toluene the modifier barely induced enantioselection (5% ee). When **18** was protonated by 20 equivalents of trifluoroacetic acid (TFA) in toluene, the same ee was obtained as in HOAc. The highest enantioselectivity in this study was achieved in the toluene/TFA mixture at 0 °C [79% ee to (*R*)-PL]. When an even bulkier α-keto ester was applied for the alkylation of **1**, the resulting diastereoisomers **20a** and **20b** had almost identical performance but they were less effective than **18**.

Finally, acylation of **1** led to a drop of ee to around 10%, independent of the presence or absence of additional functional groups (**21**–**23**). Clearly, the amide group is a poor interacting function for KPL hydrogenation. The presence of a second amino group as in **25** destroys the ee, as was observed earlier for the amino derivative of CD.[23]

The best modifier from the above screening, **18**, was chosen for a more detailed investigation of the solvent effect. The highest ee for each solvent at room temperature is shown in Table 2. Clearly, there is no correlation between the enantioselectivity and the solvent polarity characterized by the empirical solvent parameter E_T^N [45] or the relative permittivity (not shown). This behaviour is in contrast to the solvent effect found for the enantioselective hydrogenation of ethyl pyruvate [46] and KPL [17] over cinchonidine-modified Pt/Al_2O_3 where a nearly linear decrease of ee with the increase of solvent polarity was observed.

An important feature of the Pt-catalyzed enantioselective hydrogenation of activated ketones is the higher hydrogenation rate over the chirally modified Pt, compared to the unmodified catalyst.[1,2,16] An illustration of this effect in the hydrogenation of KPL is shown in Table 3. Both **18** and cinchonidine induce a substantial rate acceleration compared to the reaction over the unmodified Pt/Al_2O_3, and the effect in HOAc is bigger than that in toluene. The enhanced rate is particularly interesting when considering that a large fraction of the Pt surface sites are covered by the strongly adsorbing modifier. Note that the real nature of rate acceleration in pyruvate hydrogenation has been debated.[47]

An intriguing question is why cinchona alkaloids are more effective modifiers than **18**. We assume that a major reason for the outstanding performance of cinchona alkaloids is their strong, almost irreversible adsorption on Pt.[18,48,49] A crucial requirement an effective chiral

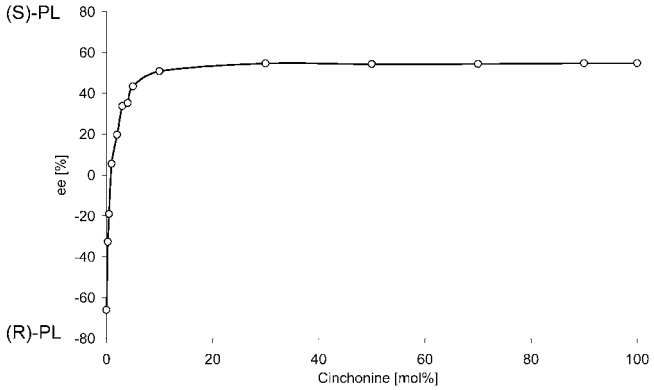


Figure 4. Non-linear behaviour of mixtures of **18** and cinchonine in the hydrogenation reaction of KPL. Standard conditions, 20 mg catalyst, 5 mL HOAc, 8 bar, full conversion.

modifier has to fulfil is the strong adsorption on the metal surface to create "chiral" sites and minimize the number of "unmodified" sites affording racemic products. In this respect, cinchona alkaloids seem to be superior to many other chiral modifiers. To estimate the relative adsorption strength of **18**, we studied the non-linear behaviour ("extended" non-linear effect, NLE)[50] of mixtures of **18** and cinchonine in the hydrogenation of KPL (Fig. 4). Cinchonine alone affords (*S*)-pantolactone and **18** gives the (*R*)-enantiomer in excess but in a modifier mixture containing less than 1 mol % cinchonine already the cinchona alkaloid dominates the enantiodifferentiation and affords the (*S*)-enantiomer in excess. It has been shown that the non-linear behaviour of modifier mixtures in Pt- and Pd-catalyzed hydrogenation reactions are basically due to their different adsorption strengths on the metal surface. [5,21,51,52] Apparently, **18** cannot compete with cinchonine for the Pt surface sites and thus can barely influence the enantiodifferentiation during hydrogenation of KPL.

The experiments shown in Figure 4 were repeated in toluene and a very similar non-linear effect was observed. This is an indication that the strikingly different efficiency of **18** in HOAc and toluene cannot be attributed to the substantially different adsorption strength of **18** on Pt in these two solvents.

Mechanistic Considerations

The mechanistic model depicted in Figure 1 has been suggested for KPL hydrogenation over cinchonidine-modified Pt/Al_2O_3.[17] In this reaction the highest ee was achieved in weakly polar solvents, e.g., toluene, and the model assumes stabilization of the half-hydrogenated state *via* formation of an N–H–O bond between the quinuclidine N and the keto carbonyl O atoms. The results in Table 1 demonstrate that applying

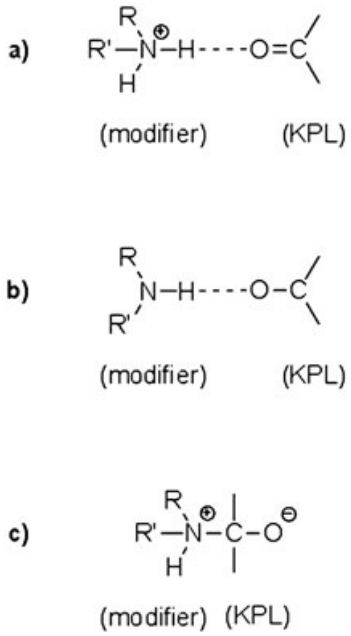


Figure 5. Possible interactions between ketopantolactone (KPL) and the chiral modifiers **1** and its amine-type derivatives, both adsorbed on the Pt surface; **a)** H bond between the amine protonated in the acidic medium and the keto carbonyl O atom; **b)** H bond between the amine and the half-hydrogenated state of the ketone; **c)** zwitterionic intermediate formed by nucleophilic attack of the amine on the keto carbonyl C atom.

1 and its amine derivatives as chiral modifiers, this type of interaction can provide only low enantioselectivity (with the exception of **4**). Good enantioselectivity is limited to acidic media where the amine-type modifiers are protonated. The importance of protonation of the N atom is corroborated by those experiments in which 20 equivalents of TFA ($pK_a = 0.2$) related to the modifier were added to toluene (Table 1, modifiers **6** and **18**). In these experiments the ee was very close to that measured in HOAc. It has been shown earlier that in (deuterated) acetone one equivalent of TFA or 24 equivalents of HOAc are sufficient to protonate the quinuclidine N of cinchonidine.[53]

On the basis of these observations we propose that in the hydrogenation of KPL on Pt modified by **1** and its amine-type derivatives the good enantioselectivity in acidic medium is due to an N^+–H–O type H bond between the protonated N atom and the keto O atom of KPL (Figure 5a). In non-acidic medium **1** and its primary and secondary amine derivatives can interact with the keto O atom of KPL *via* an H bond involving an H atom of the amine modifier (Figure 5b). This H bond is much weaker than that involving the protonated modifier[54] and the enantioselection is usually poor, with only a few exceptions (e.g., **4**). The major difference between this proposal and that suggested for cinchona-modified Pt[17] (Fig. 1) is that in non-acidic medium the primary

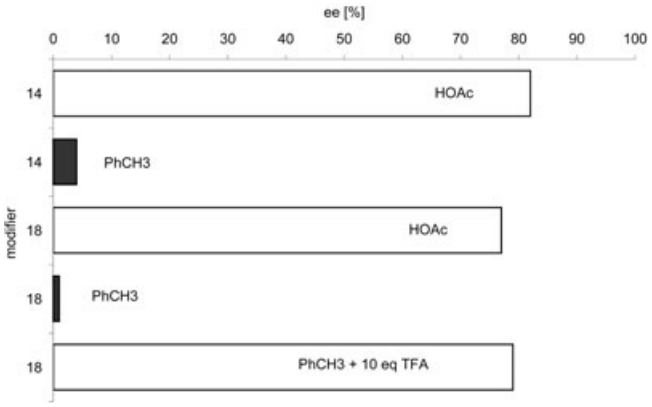


Figure 6. Maximum ee reached in the enantioselective hydrogenation of ethyl pyruvate to *(R)*-ethyl lactate on Pt/Al_2O_3 modified by **14** and **18**. The reaction conditions (*p*, *T*, amount of catalyst and solvent) had only a minor influence on the ee within the range of conditions used. Standard conditions (except for the hydrogenation in HOAc with **14**[31]): 20 mg catalyst, 10 mL solvent, conversion 65–100%.

or secondary amine modifier can interact with the substrate already before H uptake, while the role of cinchonidine (tertiary amine) is rationalized only after the half-hydrogenated state of the substrate has been formed.

A mechanistic model involving an H bond interaction between protonated cinchonidine and the activated ketone substrate has been first proposed for ethyl pyruvate hydrogenation on Pt in acidic medium.[54,55] Interestingly, in the hydrogenation of pyruvate esters in toluene or HOAc the difference between the ees on cinchona-modified Pt was only a few percent.[1,2,16] In contrast, when Pt was modified by β-isocinchonine, the opposite enantiomers of ethyl lactate formed in excess when the reactions were carried out in toluene or HOAc. [22,56]

The results in Table 1 cannot be interpreted by a recent mechanistic model based on theoretical calculations.[57] The authors assumed nucleophilic attack of the basic N atom of the modifier on the carbonyl C atom of the ketone substrate, resulting in a covalently bound zwitterionic adduct even in acidic medium (Fig. 5c). This mechanism has been adopted recently for the hydrogenation of fluorinated ketones in toluene.[58] Considering the general mechanism of ketone hydrogenation on Pt, formation of a zwitterionic adduct cannot be excluded in toluene but this reaction is unlikely in acidic medium where the reactivity of the amine is lost, particularly in the presence of the strong acid additive TFA. It has been shown that only the unprotonated amine is reactive in addition reactions with a carbonyl compound and thus the reaction rate drops rapidly below a pH of 4.[59,60] In other words, only a negligibly small fraction of the modifier adsorbed on Pt is present as a free base and can produce PL *via* this mechanism or that shown in Figure 5b; the overwhelming part of the modifier is protonated by HOAc or TFA and may interact with KPL *via* the mechanism shown in Figure 5a. Besides, formation of a zwitterion is not possible with KPL for steric reasons: the keto carbonyl C atom of KPL cannot be attacked by the N atom, because the latter would have to approach from within the lactone ring.

Finally, we compared the performance of the two best amino ester-type modifiers **14** and **18** in the hydrogenation of ethyl pyruvate under acidic and non-acidic conditions (Figure 6). The results are very similar to those achieved in the hydrogenation of KPL (Table 1): both modifiers give reasonable enantioselectivities only in acidic medium. It seems that the above mechanistic considerations can be extended to the hydrogenation of some other activated ketones over Pt modified by **1** and its various functionalized amine derivatives.

Conclusions

Various derivatives of (*R*)-1-(1-naphthyl)ethylamine **1** have been tested as chiral modifiers of Pt/Al_2O_3 in the enantioselective hydrogenation of ketopantolactone (KPL). All modifiers contain the same "anchoring moiety" responsible for adsorption on the Pt surface, and the surrounding of the N atom was varied by introducing (functionalized) alkyl and cycloalkyl groups. An ester group in the α-position to the N atom and the proper relative configuration of the side chain can significantly improve the performance of **1**. The best modifier **18**, prepared by reductive alkylation of **1** with KPL, afforded 79% ee to (*R*)-PL. An interesting point is that **1** is not alkylated by the reactant during hydrogenation, in contrast to the enantioselective hydrogenation of alkyl pyruvate where the actual modifier was **14**.[32] Still, the simple amine **1** afforded up to 52% ee to PL in acidic medium.

Most of the modifiers derived from **1** perform remarkably better in acidic medium, which suggests that a charged ammonium species is involved in the enantiodiscrimination. We propose two mechanistic models that rationalize the sometimes strikingly different ees in toluene and acetic acid. Both models assume H bond formation between the amine-type modifier and the O atom of the activated ketone substrate, and the H atom originates from the amine and not from the substrate ("half-hydrogenated state"). Good enantioselectivity is attributed to an N^+-H-O type hydrogen bond in acidic medium.

We hope that the present results will guide us to new, more efficient synthetic modifiers for Pt and pave the way to successful catalyst systems for a broader range of substrates and reactions.

Experimental Section

Ketopantolactone (KPL, Roche), and the commercial modifiers **1** (Acros), **2**, **3, 23** and **24** (all purchased from Aldrich), **8** (Fluka) and cinchonine (Fluka) were used without further purification. Toluene (J. T. Baker) was dried and stored over activated molecular sieve. HOAc (Fluka) was used as received and the other solvents were dried according to standard procedures.

Catalytic Hydrogenation of Ketopantolactone

A 5 wt % Pt/Al_2O_3 catalyst (Engelhard 4759) was used for all experiments. Before use the catalyst was prereduced at 673 K for 1 h in flowing hydrogen and cooled to room temperature under flowing hydrogen for 30 min. After flushing with Ar the catalyst was first contacted with the solvent, containing the proper amount of modifier. The hydrogenation was carried out in a stainless steel autoclave equipped with a glass liner and PTFE cover. Dispersion of Pt after heat treatment was 0.4, as determined by transmission electron microscopy.

Under standard conditions, 10–20 mg of prereduced catalyst, 5–10 mL dry solvent, 6.8 μmol modifier and 236 mg KPL (1.84 mmol) were used at room temperature. The reaction mixture was magnetically or mechanically stirred at 500 min^{-1} or faster. The products were analyzed by gas chromatography at full conversion, which was usually reached after 0.5–3 h. The enantiomeric excess (ee) was determined with a HP 5890A gas chromatograph using a Chirasil-DEX GB (Chrompack) capillary column.

Synthesis of Modifiers

Syntheses of modifiers **14**–**17**,[32] **21**,[61] and **20a** and **20b**[44] have been published elsewhere. All new modifiers were synthesized from **1** and the corresponding carbonyl compound *via* reductive alkylation (see Supporting Information). The preferred method was formation of the imine in titanium(IV) isopropoxide and reduction with $NaBH_3CN$. Only in the case of **6** $LiAlH_4$ had to be used instead. Diastereomers could be separated by flash chromatography. Modifiers **12** and **13** were prepared from **14** and **17**, respectively.

Modifiers **16** and **17** were obtained in a ratio of 26:74 and were separated by flash chromatography (ethyl acetate:hexane = 1:10 with addition of triethylamine). The diastereomers were identified, compound **17** eluted first off the column. The absolute configuration of the diastereomers **16** and **17** was assigned by comparison between the experimental spectra of the fractions obtained after column chromatography and the VCD spectra calculated using the density functional theory (DFT). The experimental VCD spectra were measured on a Bruker PMA 37 accessory coupled to a VECTOR/33 Fourier transform infrared spectrometer. Spectra were recorded in $CHCl_3$ using a transmission cell equipped with KBr windows and a 1 mm Teflon spacer. The theoretical spectra were determined as follows: first the conformational space of **16** and **17** was studied, in order to identify the most stable conformers, and among them only those were selected whose energy differed from the lowest value by less than 0.5 kcal/mol. The level of theory used for the optimizations, that comprised all degrees of freedom, was B3LYP and B3PW91 hybrid functionals and 6–31G(d, p) basis set. Rotational strengths were then calculated at the same level of theory and a synthetic spectrum was generated using Gaussian functions centred at the excitation energies and scaled with the calculated rotational strengths. All calculations were performed with the Gaussian 98 program package.[62] The reliability of this method of assigning of the absolute configuration was verified by comparing experimental and calculated spectra of pentahelicene.[63]

Supporting Information

Experimental procedures and spectral data for all new modifiers are available.

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