Chiral nitrogen compounds as new modifiers for the enantioselective hydrogenation of ethyl pyruvate

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The enantioselective hydrogenation of ethyl pyruvate to (R)- or (S)-ethyl lactate has been studied over alumina- and carbon-supported Pt-metal catalysts modified by various heterocyclic N-compounds and substituted amides. The reactions were carried out under mild conditions in acetic acid; other solvents had a detrimental effect on enantioselectivity. An enantiomeric excess (ee) of 67% and a rate acceleration by a factor of 6, compared to the unmodified catalyst, was observed with alumina-supported Pt modified by (R)-1-(1-naphthyl)ethylamine. In contrast, carbon-supported Pd, Ru and Rh were non-selective and only little active. The studies indicated that besides naphthyl or quinolyl groups, two separate phenyl groups or one phenyl group together with two amino groups can provide a suitable anchoring of the chiral modifier on the Pt surface. The nature of interaction between the modifiers and ethyl pyruvate is briefly discussed.

Keywords: enantioselective hydrogenation; chiral modifier; ethyl pyruvate; Pt/alumina

1. Introduction

In the solid-catalyzed enantioselective hydrogenation reactions chiral information is usually transferred by a preadsorbed chiral molecule of natural origin [1]. The enantioselective hydrogenation of ethyl pyruvate (EP) to (R)-ethyl lactate (scheme 1) is one of the most studied reactions [2–5]. 88–95% enantiomeric excess (ee) has been obtained using Pt/alumina modified by cinchonidine and some of its simple derivatives [6].

Earlier investigations indicated that any change either in the structure of the cinchona alkaloid modifier, the catalyst or the reactant resulted in a drop in ee [3,7,8]. These studies also revealed that the crucial structural parts of the cinchona alkaloids are the aromatic moiety for anchoring the modifier on the Pt surface, the stereogenic region for chiral induction and the basic nitrogen (or its protonated

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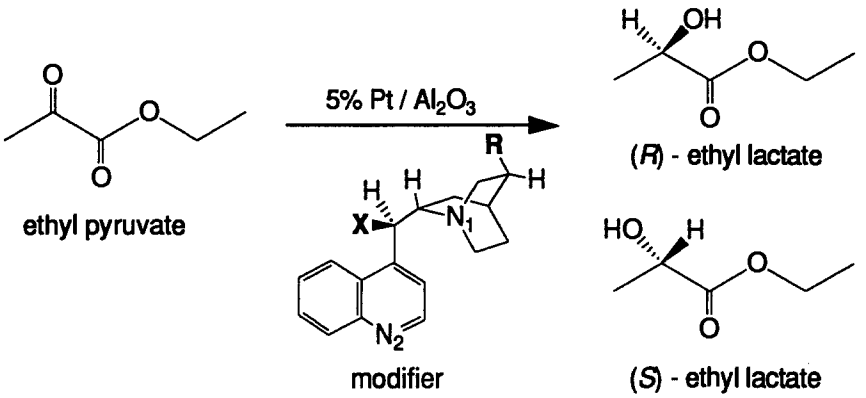
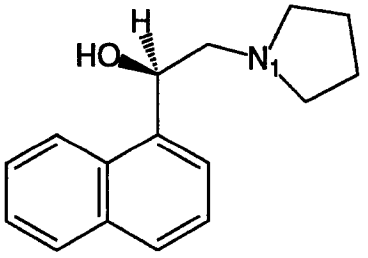


	R	X
cinchonidine	C_2H_3	OH
10,11-dihydrocinchonidine	C_2H_5	OH
10,11-dihydro-*O*-methylcinchonidine	C_2H_5	OCH_3

Scheme 1.

form) for interaction with the reactant. Based on this information, new, structurally simple chiral amino alcohol type modifiers [9,10] have been synthesized recently. One of them, (R)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (PNE) (scheme 2), afforded ee as high as 75% [10].

In a further attempt to obtain more information on the possible mechanism of enantiodifferentiation, we tested several N-containing chiral compounds as modifiers for the enantioselective hydrogenation of α-ketoesters. All three important structural parts of the modifiers were varied, using this time commercially available chiral compounds. Here, we show five of them which extend the structural variety of possible modifiers for the hydrogenation of EP to ethyl lactate as a model reaction.



(*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (**PNE**)

Scheme 2.

2. Experimental

The following N-containing modifiers have been used (bold numbers refer to the formula in table 1): (R)-1-(1-naphthyl)ethylamine (**2**, Fluka); (S)-1-(1-naphthyl)-ethylamine (**3**, Fluka); (5R, 11R)-(+)-2,8-dimethyl-6H, 12H-5,11-methanodibenzo[b,f][1,5] diazocin ("Tröger's base") (**4**, Fluka); (R)-(−)-1-(1-naphthyl) ethylisocyanate (**5**, Merck); (R)-1-(4-nitrophenyl)ethylamine hydrochloride (**6**, Fluka); (R)-(+)-N-(α-methylbenzyl)phthalic acid monoamide (**7**, Fluka) and D(+)-α-methylbenzylamine (**8**, Fluka). Ethyl pyruvate (EP, Aldrich) was freshly distilled under vacuum before each reaction. The metal dispersion of the 5 wt% Pt/alumina catalyst (Engelhard 4759) was 0.22, as determined by CO chemisorption [11]. Under standard conditions, the catalyst was prereduced before use at 400°C for 2 h in 30 ml min^{-1} flowing hydrogen, then transferred to the reactor under solvent with the exclusion of oxygen.

The hydrogenation of EP was carried out in a 100 ml stainless steel autoclave equipped with a 50 ml glass liner and PTFE cover. In the general procedure, 100 mg catalyst, 10 ml (0.09 mol) EP, 6.2 μmol modifier and 20 ml acetic acid were used. The reaction mixture was magnetically stirred with 1250 rpm in 10 bar hydrogen at room temperature. Enantiomeric excess, expressed as ee (%) = 100 ([R] − [S])/([R] + [S]), and conversion were determined with a HP 5890A gas chromatograph, using a WCOT Cyclodextrin-β-2,3,6-M-19 (Chrompack) capillary column with a reproducibility of ±1%.

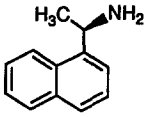
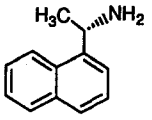
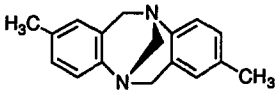
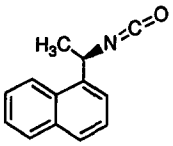
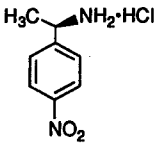
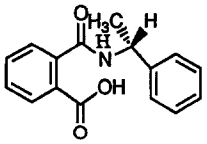
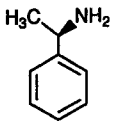
3. Results

Table 1 shows the rate and ee of ethyl pyruvate (EP) hydrogenation over 5 wt% Pt/alumina modified with various chiral N-compounds. The highest ee and rate acceleration, compared to the unmodified reaction, was observed in the presence of a chiral alkylaromatic primary amine (**2**). Structurally rather different modifiers, the N-heterocyclic tertiary amine **4** and the alkyl-aromatic isocyanate **5** provided almost the same ee in acetic acid. Note that until now only 1,4-aminoalcohol type chiral compounds have been reported to induce enantioselectivity in this reaction [1].

An important observation is that using the (S)-enantiomer **3** instead of the (R)-enantiomer **2**, the product distribution also changes from an excess of (R)-ethyl lactate to (S)-ethyl lactate, whereas the absolute value of ee remains almost the same. A similar change in product distribution has been reported when cinchonidine (C-8 (S), C-9 (R)) was substituted to its near-enantiomer cinchonine (C-8 (R), C-9 (S)) [12,13].

The influence of solvents on the rate and enantioselectivity is rather unusual. It seems that the enantioselective reaction is limited to acetic acid; other common polar or apolar solvents afforded low or hardly any ee. In contrast to this observa-

Table 1
Enantiomeric excess (ee), initial rate (r_0) and conversion measured in various solvents using novel chiral modifiers and 5 wt% Pt/alumina (Engelhard 4759)

No.	Modifier	Solvent	ee (%)	Conversion after 2 h (%)	r_0 (mmol g^{-1} h^{-1})
1	unmodified	AcOH	–	30	121
2		AcOH	67	98	730
		EtOH	29	30	125
		toluene	10	38	157
3		AcOH	−65	81	690
4		AcOH	65	70	432
		EtOH	2	24	127
		toluene	4	27	143
5		AcOH	59	40	350
6		AcOH	29	30	126
7		AcOH	23	25	133
8		AcOH	0	20	94

tion, in the hydrogenation of EP catalyzed by cinchona- or PNE-modified Pt with acetic acid, toluene or ethanol used as solvent, the reaction rates and enantioselectivities were found to be comparable [10,14].

With the cinchonidine modified catalyst, a linear correlation between ee and reciprocal initial rate [15] was observed, as predicted for a ligand-accelerated reaction [16]. There is no clear correlation between ee and initial reaction rate, when using acetic acid as a solvent and any of the modifiers **2–7**, as shown in table 1. Considering the standard deviation of the determination of initial rate (ca. ±6%), an unambiguous rate acceleration due to the presence of modifier was observed only when ee was about 60% or higher.

The influence of catalyst composition was tested using the best modifier **2** in acetic acid. The catalysts contained 5 wt% noble metal on various supports. The reaction rates and enantioselectivities are presented in table 2. Only Pt catalysts showed enantioselectivity, but there are great differences in initial rate and ee, depending on the nature of support (carbon, alumina or titania), Pt content (5 or 10 wt%) and pretreatment temperature (up to 400°C). Note that the catalyst screening results listed in table 2 do only reflect major tendencies. Careful optimization of catalyst composition and pretreatment conditions may significantly improve the catalytic behaviour of the differently modified catalysts.

Table 2
Influence of ETPY hydrogenation modified with (R)-(+)-1-(1-naphthyl)ethylamine (**2**) on enantiomeric excess (ee), initial rate (r_0) and conversion, using acetic acid as a solvent and 5 wt% noble metal catalysts

No.	Metal	Support	Prereduction temp. (°C)	Conversion [a] (%)	r_0 (mmol g^{-1} h^{-1})	ee (%)
1	Pt [b]	Al_2O_3	300	90	600	72
2	Pt [b]	Al_2O_3	–	50	225	30
3	Pt [b]	Al_2O_3	400	98	730	67
4	Pt [c]	TiO_2	400	20	70	42
5	Pt [d]	Al_2O_3	400	45	465	23
6	Pt [e]	Al_2O_3	400	90	730	65
7	Pt [f]	C	300	97	906	31
8	Pd [g]	C	300	5	48	0
9	Rh [h]	C	300	<1	<1	0
10	Ru [i]	C	300	<1	<1	0

[a] Measured after 2 h.
[b] Engelhard 4759.
[c] Aerogel sample Pt5PC (calcined in air at 400°C for 5 h) [17].
[d] 10 wt% Pt/Al_2O_3 (Fluka 80990).
[e] Johnson Matthey 27123.
[f] Engelhard Escat 22.
[g] Johnson Matthey 5R58/60.
[h] SSF (Schweizerische Sprengstoff- Fabrik).
[i] Degussa H 101 B, 4/682.

4. Discussion

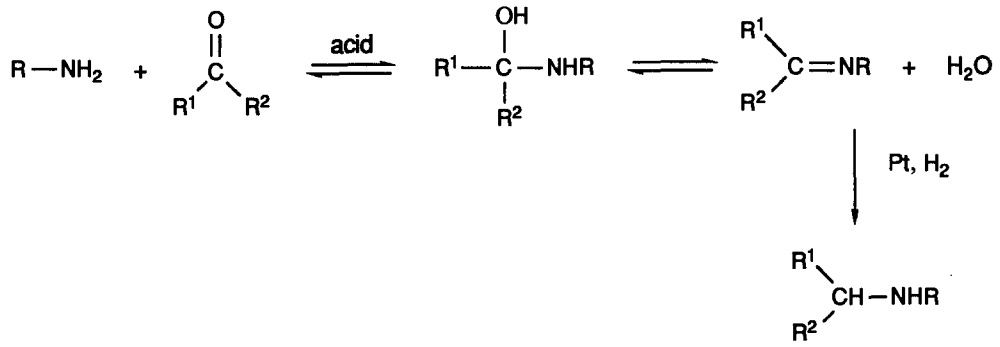
When attempting to interpret the good ee observed in the presence of some new modifiers, we have to discuss first the stability of the chiral N-compounds **2**–**7** before or during EP hydrogenation. Only modifiers **4** and **7** are assumed to be stable under the mild reducing conditions. The partial hydrogenation of the naphthalene ring under these reaction conditions has been proved earlier [10], but the saturation of phenyl groups is negligible at room temperature.

The primary amine modifiers **2**, **3** and **6** rapidly condense with the activated carbonyl group of EP, and the imines are reduced on Pt to secondary amines according to scheme 3.

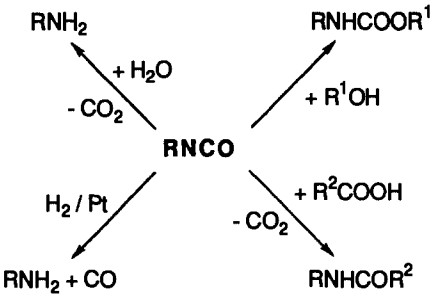
The latter seems to be the real structure of these modifiers, as the further alkylation of secondary amines necessitates elevated temperatures [18]. The nitro group of **6** is expected to be reduced to an amino group before the reduction of EP [19].

The reactivity of **5** is also high, but it is not simple to predict the product composition. Scheme 4 shows that isocyanates can react under mild conditions with water, alcohols or carboxylic acids, and can be reduced on Pt [20–22].

We propose that **5** is transformed to naphthylethylamine (**2**) before EP hydrogenation by reduction on the prereduced Pt or by hydrolysis with the small amount of water present in the solvent AcOH. In the former reaction equimolar amount of CO is formed, which explains the lower reaction rate observed in the presence of **5**, compared to **2** or **3**. Heating the modifier **5** in 0.5 ml acetic acid to 100°C for about 10 min results in the formation of the corresponding amide [20]. Using this compound as a chiral modifier, we obtained only 36% ee, which confirms that not the corresponding amide is the real structure of **5** during EP hydrogenation. A careful analysis of the chemical nature of modifiers **2**–**7** after the hydrogenation reaction is planned to supply unambiguous information for the interpretation of enantiodifferentiation. Note that the unusual solvent effect observed in this reaction is likely due to the positive effect of acetic acid on the formation of the "real" modifier and the absence of this effect, when using toluene or ethanol.



Scheme 3.

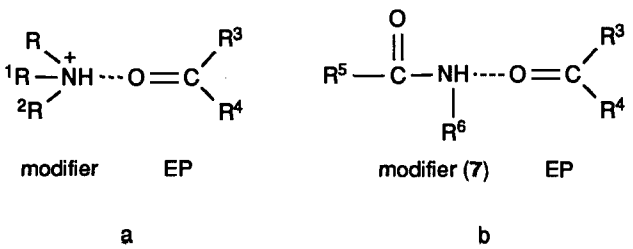


Scheme 4.

There are different mechanistic concepts developed for the interpretation of enantiodifferentiation observed in the hydrogenation of α-ketoesters with cinchonidine-modified Pt [23–26]. Based on a theoretical study, it was proposed recently [25] that in acetic acid cinchonidine protonated at N-1 interacts with the O atom of the α-carbonyl moiety of the pyruvate ester (scheme 5a), both adsorbed on the Pt surface. The crucial N–H–O interaction in the energetically favourable complex is developed as H-bonding between modifier and reactant, but also resembles the half-hydrogenated state of the reactant.

One of the new modifiers (**7**) is not an amine but a substituted amide. The amides, especially the aromatic amides, are weakly acidic [27]. We propose that the moderate ee is again due to the formation of an N–H–O interaction: H-bonding between the amido group of the modifier and the O atom of the α-carbonyl group of EP (scheme 5b), both adsorbed on the Pt surface. A H-bond between the strongly acidic carboxyl group of the modifier and the α-carbonyl group is not likely to induce enantiodifferentiation, as the carboxyl group is too far from the stereogenic center.

Until now, only those chiral compounds have been reported to be efficient modifiers for α-ketoester hydrogenation, which possess a quinolyl or naphthyl anchoring group [7,9,10]. The results gathered in table 1 indicate that modifiers with two separate phenyl groups or one phenyl group with two strongly adsorbing amino groups are also suitable for anchoring the modifier on the Pt surface, which is a



Scheme 5.

prerequisite for enantiodifferentiation. For comparison, one phenyl group with only one amino group (**8**, instead of **6**) provides no ee under the same conditions.

There are contradictory explanations concerning the role of the O atom (with its two non-bonding electron pairs) in the 1,4-aminoalcohol type modifiers, such as cinchonidine or cinchonine [24–26]. We proposed [25] that an interaction via the OH group of the modifier (electron pair donation to the carbonyl C atom of EP) is less likely than the above discussed N–H–O interaction. On the contrary, Augustine et al. [24] assumed the formation of a six-membered ring by nucleophilic attraction between the oxygen at C-9–OH of cinchonidine and the ester oxygen of EP, as well as N-1 of cinchonidine and the keto C atom. In other words, the same importance has been attributed to O and N atoms of the modifier. Modifier **4** is the first chiral compound reported, which does not possess OH (or O atom) and is still able to induce considerable enantiodifferentiation in the hydrogenation of EP. The 65% ee observed in the presence of **4** demonstrates that the interaction between the protonated amine modifier and the activated carbonyl group of the reactant is sufficient for enantiodifferentiation, provided that the modifier adsorbs strongly (in a fixed position) on the Pt surface.

Acknowledgement

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