JOURNAL OF CATALYSIS 154, 371–378 (1995)

A Novel Aminoalcohol Modifier for the Enantioselective Hydrogenation of Ethyl Pyruvate on Pt/Alumina

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Received October 3, 1994; revised February 17, 1995

A novel chiral modifier, (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl) ethanol (PNE), has been synthesised and tested in the enantioselective hydrogenation of ethyl pyruvate over Pt/alumina. An enantiomeric excess in (*R*)-ethyl lactate of up to 75% was achieved. The influence of solvent, pressure, temperature, and concentrations of the components (reactant, modifier, catalyst) on the reaction rate and enantiodifferentiation was investigated. Among various polar and nonpolar solvents, acetic acid was found to be most suitable for reaching good enantioselectivity. Favorable reaction conditions are 1–10 bar hydrogen pressure, 0–25°C, and a catalyst loading ≥ 15 g liter^{-1}. The efficiency of PNE is demonstrated by the very low modifier : reactant molar ratio (1 : 30,000) which is required to obtain maximum enantioselectivity. The performance and stability of the aminoalcohol-type modifier are compared to those of cinchona alkaloids. At low hydrogen pressure, the enantiodifferentiation of PNE is comparable to that of 10,11-dihydrocinchonidine.

INTRODUCTION

The enantioselective hydrogenation of α-ketoesters to the corresponding α-hydroxyesters (Scheme 1) on platinum catalysts modified with cinchona alkaloids, originally reported by Orito and co-workers (1), is one of the few examples where technically interesting enantioselectivities are reached using a heterogeneous catalyst (2–4). Enantiomeric excesses (ee) of nearly 90% have been reported for the hydrogenation of ethyl benzoylformate to (*R*)-(−)-ethyl mandelate (R = phenyl) using a Pt/C catalyst modified with cinchonidine (5). In the hydrogenation of ethyl pyruvate to (*R*)-ethyl lactate (R = CH_3) on a Pt/alumina catalyst modified with 10,11-dihydro-*O*-methylcinchonidine, an ee of 95% has been reported by Blaser *et al.* (6).

Considerable effort has been expended in the past years to gain insight into the mechanism of enantiodifferentiation (7–9). As a result of this effort, three different enantiodifferentiation models have been proposed for the hydrogenation of α-ketoesters on cinchonidine-modified Pt. The three models have been compared and critically discussed in a recent study (10).

The known heterogeneous catalyst systems are highly specific to the reactant, modifier, and catalyst and sensitive to changes in the reaction conditions, a behaviour which is known for enzymatic reactions (11). Until now, only the Pt–cinchona system has afforded the hydrogenation of α-ketoesters and α-ketoacids (12) with high enantioselectivity. The use of Rh or Ir yields moderate ee (around 30%) and Pd, Ru, and Raney Ni were found to be nonselective (11, 13). When the activating functional group next to the carbonyl moiety is changed from an ester carbonyl to a keto carbonyl group, only 38% ee is obtained over Pt/silica modified by cinchonidine (14). Structural alterations of cinchonidine (Scheme 2) at various positions led to significant changes in the enantioselectivity of the reaction. Alkylation of the quinuclidine nitrogen N-1 resulted in a complete loss of enantioselectivity (15), which indicates that this center plays a crucial role in the mechanism of enantiodifferentiation (15, 16). Upon partial hydrogenation of the quinoline ring, selectivity drops below 50% (15, 17). The OH group in the 1,4-position to the N-1 nitrogen, or rather the stereogenic center at C-9, seems also to be important. The selectivity is hardly influenced by O-methylation, whereas replacing the OH by hydrogen or using the acylated derivative results in a decrease in ee to 20–44% (15). Other natural compounds and their derivatives, such as ephedrine, strychnine, codeine, brucine, and proline, have also been tested, but the observed enantioselectivities are rather low (18–20).

Here we propose a different strategy which may form the basis for an extension of the range of applicability of this chiral hydrogenation system. Instead of modifying cinchonidine (15), we synthesised new, structurally simple chiral amino alcohol modifiers, which possess the cru-

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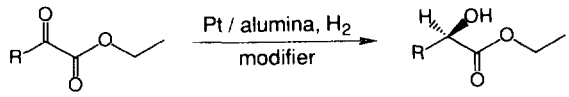
0021-9517/95 $12.00



SCHEME 1

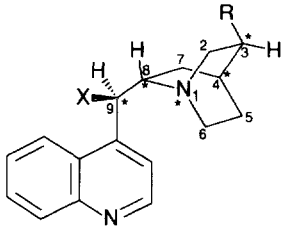
cial structural parts, such as the aromatic ring as anchoring group, the chiral moiety, and the basic nitrogen. We hope that through this strategy new aspects of reactant–modifier–solid surface interaction will be uncovered and a step towards designing the structure of chiral modifiers can be made.

The synthesis of chiral aminoalcohols possessing an aromatic group in the neighbourhood of the stereogenic center and different substituents at the N-function is reported elsewhere (21, 22). Preliminary tests indicated that one of these modifiers, (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (PNE) (Scheme 3), is a promising candidate for substituting cinchonidine in the enantioselective hydrogenation of ethyl pyruvate to (*R*)-ethyl lactate. Here we report a detailed kinetic study of the reaction using this new synthetic modifier.

EXPERIMENTAL

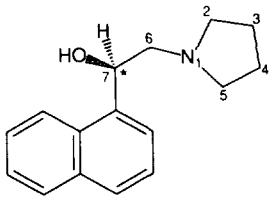
The 5-wt% Pt/alumina catalyst (Engelhard 4759) was prereduced at 400°C for 1.5 h in 30 ml min^{-1} flowing hydrogen. The metal dispersion as determined by CO chemisorption (23) was 22%. Ethyl pyruvate (Aldrich) was freshly distilled under vacuum before each reaction. The synthesis of PNE is reported elsewhere (21, 22).

The hydrogenation of ethyl pyruvate was carried out in a 100-ml stainless steel autoclave. A 50-ml glass liner with a Teflon cap and a Teflon stirrer was used to keep the system inert. If not otherwise stated, the following standard conditions were used: 100 mg catalyst, 1.5 mg (6.22 μmol) PNE, 10 ml (0.09 mol) ethyl pyruvate, and 20 ml acetic acid. The prereduced catalyst was transferred, with the exclusion of oxygen to the reactor. The



	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 2. (*R*)-2-(1-*P*yrrolidinyl)-1-(1-*n*aphthyl)*e*thanol (PNE).



SCHEME 3

reaction mixture was stirred magnetically at 25°C under 10 bar hydrogen pressure at 1250 rpm. A Lauda RKT 20 cryostat was used for reactions performed below 0°C. Reaction temperatures referred to in the text represent the controlled temperature of the bath in which the autoclave was immersed.

The hydrogenation of the modifier in the absence of ethyl pyruvate was carried out at 1 and 25 bar at 25°C with a constant modifier : catalyst weight ratio of 1.6×10^{-4}. The product was isolated after reduction and identified by NMR and MS. The 300-MHz ^1H NMR and the 75-MHz ^{13}C NMR spectra were measured in $CDCl_3$.

Enantiomeric excesses and conversions were determined by an HP 5890A gas chromatograph using a WCOT fused-silica capillary column with a CP-cyclodextrin-β-2,3,6-M-19 chiral phase. ee (%) is defined as the absolute value of $100 \times ([R] - [S])/([R] + [S])$. The standard deviation of the analysis was less than $\pm 0.5\%$.

RESULTS

Preliminary tests of the catalyst system with (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)-ethanol as modifier indicated that the parameters decisive for the catalytic performance are the solvent, the concentrations of the components (reactant, modifier, and catalyst), temperature, and pressure. Consequently we concentrated on these parameters in our kinetic study. As catalyst, we used 5-wt% Pt/alumina because it was found to be superior to Pd and Ru catalysts.

Catalyst Loading

Figure 1 shows the influence of catalyst concentration on ee and reaction rate in acetic acid. The modifier : catalyst ratio was kept constant at 0.062 mmol g^{-1}. Note that there is a linear relationship between reaction rate and catalyst concentration below 15 g $liter^{-1}$. Mass transport phenomena start to influence the overall rate above this critical value. The mass transfer coefficient k_m, calculated from the reverse ($1/r$ vs $1/m$) plot, amounted to $8.2 \times 10^{-3}\ s^{-1}$. As a consequence of this result, a catalyst loading of 3.3 g $liter^{-1}$ was chosen for all subsequent studies, which allows the reactor to work in the kinetically controlled region. Enantioselectivity slightly increases with ascending amount of catalyst and reaches a plateau at

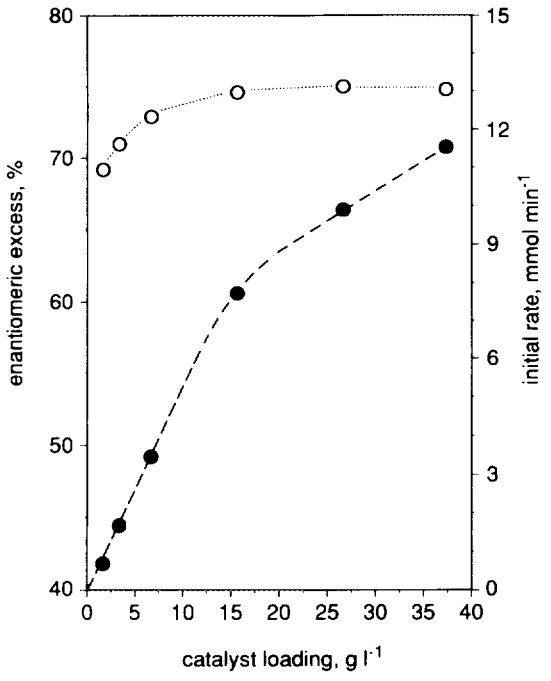


FIG. 1. Enantiomeric excess (ee) (○) and initial rate (●) as a function of catalyst loading in acetic acid.

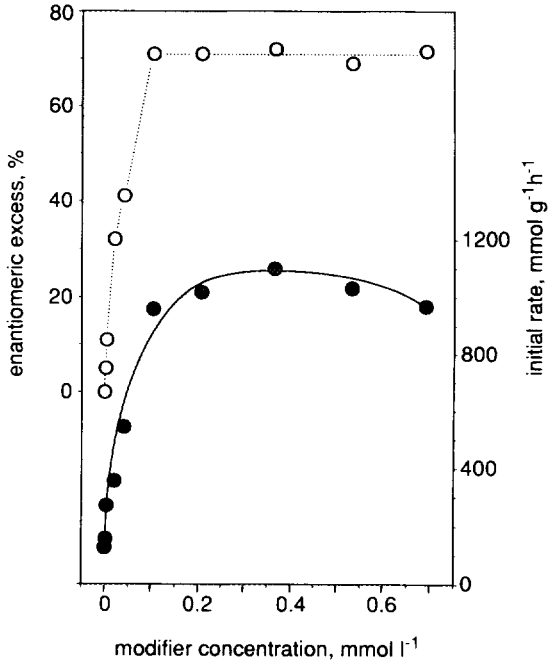


FIG. 2. Enantiomeric excess (ee) (○) and initial rate (●) as a function of modifier concentration in acetic acid.

75%. The increasing effect of mass transfer above a catalyst concentration of 15 g liter^{-1} seems to have no significant influence on the enantioselectivity, whereas the relative augmentation of hydrogen supply at low catalyst concentrations raises the extent of nonselective hydrogenation, leading to racemic product.

Modifier Concentration

The influence of modifier concentration on initial rate and ee is illustrated in Fig. 2. Both rate and selectivity increase with increasing modifier concentration and reach a plateau or a broad maximum above 10^{-4} *M*. The initial rate is accelerated by a factor of 7–8 over to the unmodified hydrogenation of ethyl pyruvate. The 10^{-4} *M* modifier concentration corresponds to modifier : reactant molar ratio of 1 : 30,000. Assuming a Pt(111) surface and flat adsorption of ethyl pyruvate and of the naphthalene ring of the modifier, one PNE–pyruvate complex would occupy about 20 surface Pt atoms, as model calculations indicate (22). A formal calculation based on the dispersion of Pt (D = 0.21) revealed that about 10% of the applied modifier is sufficient to cover the surface Pt atoms. Unfortunately, the fraction of PNE adsorbed on Pt or on the alumina support is yet unknown.

Reactant Concentration

In Fig. 3, the enantiomeric excess shows a slight maximum as a function of ethyl pyruvate concentration at about 4.5 *M*. For all measurements, the total reaction volume was kept constant at 30 ml. The decrease in selectivity when working without solvent (c = 9.1 *M*) can be explained by the general solvent effect, as discussed later.

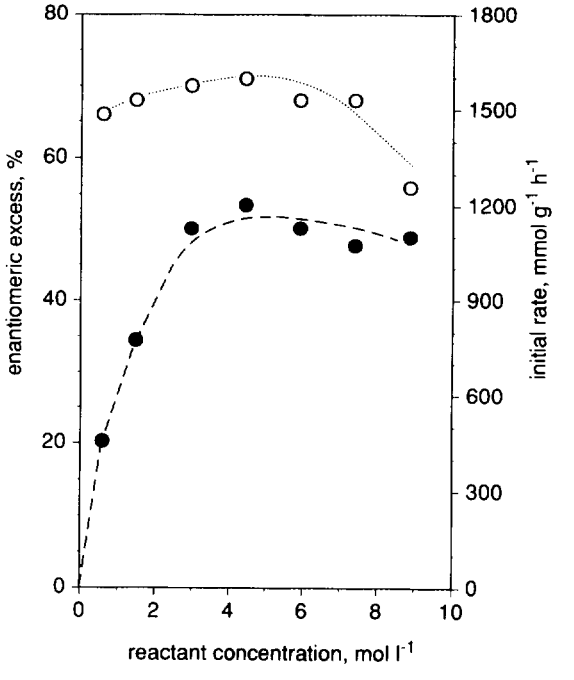


FIG. 3. Influence of reactant concentration on ee (○) and initial rate (●) in acetic acid. Note that c = 9.1 *M* corresponds to pure ethyl pyruvate without solvent.

The initial slope of the rate–concentration curve indicates that at a low reactant concentrations, the reaction follows near first-order kinetics with respect to the reactant. Above 3 *M*, the rate is practically independent of reactant concentration (zero-order).

Solvent Polarity

The hydrogenation of ethyl pyruvate was carried out in various solvents in order to study the influence of solvent polarity on ee and initial rate. The empirical solvent parameter E_T^N (24) was chosen as a measure for the solvent polarity. As shown in Fig. 4, both rate and enantioselectivity decrease with increasing E_T^N from 0 to 0.5. In the range 0.6–1.0 no correlation is found. The likely interpretation is that these polar solvents (special symbols ◆, ◇ in Fig. 4) are not chemically inert towards the reactant or the modifier. In acetic acid, in which the highest ee among all the tested solvents were obtained, the modifier is protonated. The protonation of the N-1 atom of cinchonidine has been shown to have a substantial influence on the mechanism of enantiodifferentiation (9). There is also a probability of rate acceleration in acetic acid due to general acid catalysis of carbonyl reduction (25). It has been proved by NMR and UV spectroscopic measurements (26) that in primary alcohols the reactant is mainly present as its hemiketal. Finally, considerable hydration of ethyl pyruvate (27) can be expected in water.

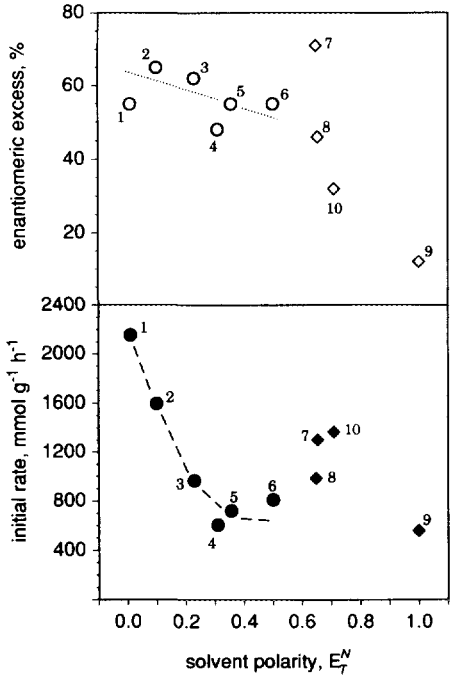


FIG. 4. Correlation between empirical solvent parameter E_T^N and ee (top) or initial rate (bottom) measured in various solvents: (1) *n*-hexane, (2) toluene, (3) ethyl acetate, (4) dichloromethane, (5) acetone, (6) cyclohexanol, (7) acetic acid, (8) ethanol, (9) water, and (10) ethanol/water = 8/2 (volume ratio). ◇, ◆, Polar solvents.

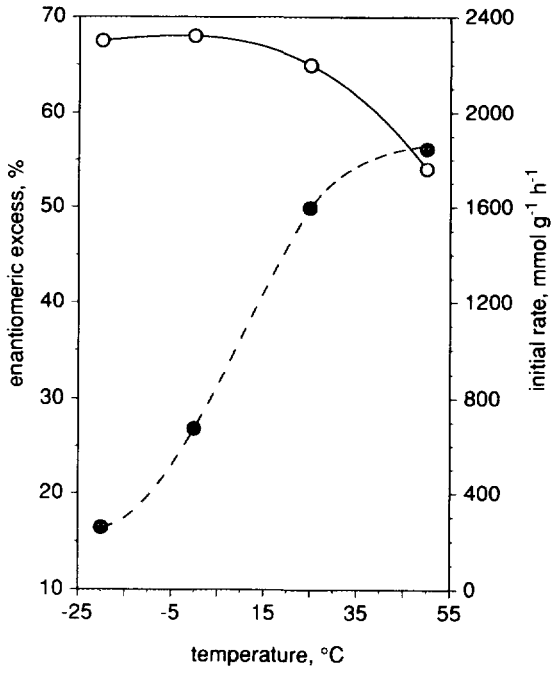


FIG. 5. Influence of reaction temperature on ee (○) and initial rate (●) in toluene under standard conditions.

Reaction Temperature

The temperature dependence of the reaction (Fig. 5) was investigated in toluene rather than acetic acid because of the high melting point of acetic acid (16.7°C). The enantioselectivity reaches a maximum at 0°C and decreases rapidly at temperatures above 25°C. The expected exponential increase of the initial rate with ascending temperature is distorted by decay above room temperature. The reason for this behaviour is discussed below.

Prehydrogenation of the Modifier

In order to determine the reason for the loss of ee above room temperature, we changed the catalyst pretreatment procedure. After reduction of the dry catalyst at 400°C in flowing hydrogen, the modifier and solvent were added and the slurry was mixed for 1 h at 10 bar hydrogen at various temperatures. Then ethyl pyruvate was added and its hydrogenation was carried out at 25°C and 10 bar (standard conditions). The influence of the prehydrogenation temperature in toluene is illustrated in Fig. 6. At 0°C, the selectivity is about the same with or without prehydrogenation of the modifier. However, at 25 and especially at 50°C, the prehydrogenation of the modifier results in a considerable loss in ee compared to the reactions without prehydrogenation. This is a clear indication

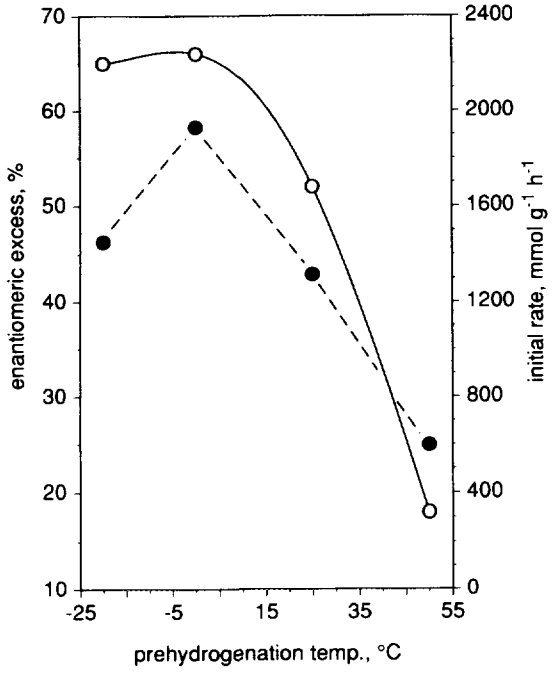


FIG. 6. Enantiomeric excess (ee) (○) and initial rate (●) as a function of prehydrogenation temperature in toluene under standard conditions.

that the PNE modifier is not stable on the Pt surface at 10 bar and 25°C or above. The higher ee obtained at 25 or 50°C without prehydrogenation is likely to be due to the higher stability of PNE towards hydrogenation at the naphthalene ring in the presence of ethyl pyruvate (competitive hydrogenation; see below).

Astonishingly, the initial rate of pyruvate hydrogenation as a function of prehydrogenation temperature shows almost the reverse behaviour to that shown in Fig. 5. The likely explanation for the descending reaction rate with increasing prehydrogenation temperature above 0°C is again the partial hydrogenation of the modifier (cessation of enantiodifferentiating and rate accelerating effect). We propose that the unexpected rate acceleration effect (by a factor of >3) observed after prehydrogenation of the catalyst and modifier at 0°C in toluene is due mainly to the cleaning of the Pt surface. The hydrogen treatment of the catalyst at 400°C can remove many surface impurities. This reductive surface cleaning procedure seems to be completed during the hydrogen treatment in toluene (competitive hydrogen adsorption and "washing out" of the impurities). Repeating the reaction with a prehydrogenation step at 0°C in the absence of modifier resulted also in higher initial rates (by a factor of 2).

Hydrogen Pressure

The pressure dependence shown in Fig. 7 indicates that, at hydrogen concentrations higher than 10 bar, selectivity drops to about 55%. NMR analysis of the products proved that the unsubstituted naphthalene ring of PNE was hydrogenated under reaction conditions, whereas the substituted aromatic ring remained unaffected. The conversion to (5,6,7,8)-tetrahydro-PNE increased from about 5% at 1 bar (1 h) to 60% at 25 bar (1.3 h). The large fluctuations of ee and initial rate in this series are probably due to difficulties in controlling the competitive hydrogenation of ethyl pyruvate and PNE.

The observed hydrogenation of PNE is not unexpected. It is known (28) that naphthalene derivatives can be partially hydrogenated under such conditions, the extent of reaction being a function of their structure and the specific reaction parameters.

Rate-Accelerating Effect

The rate acceleration observed in the hydrogenation of ethyl pyruvate in the presence of PNE may be attributed to the following effects: (i) base catalysis of the carbonyl reduction; (ii) suppression of side reactions (e.g., polymerisation of ethyl pyruvate) and the strong adsorption of some impurities, and (iii) special interaction with the reactant or the reaction intermediate ("ligand-accelerated" reaction (29)).

In order to discover the origin of rate acceleration, the racemic hydrogenation of ethyl pyruvate was repeated in the presence of various additives. Table 1 shows their influence on conversion and on initial rate. The application of *N*-methyl- or *N*-(2-hydroxyethyl)pyrrolidine as tertiary N bases resulted in lower rates in both solvents,

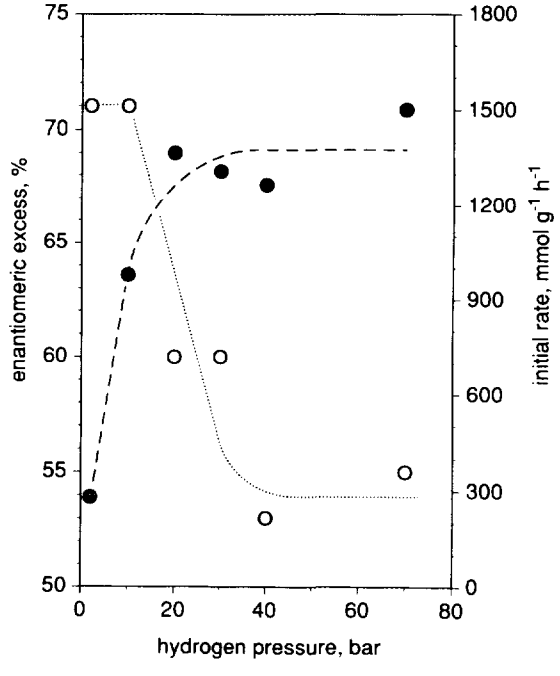
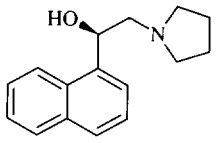
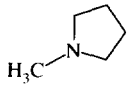
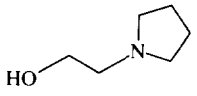
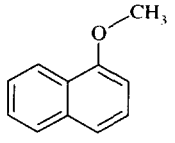
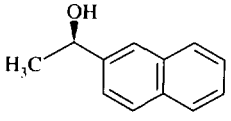


FIG. 7. Enantiomeric excess (ee) (○) and initial rate (●) as a function of hydrogen pressure in acetic acid under standard conditions.

TABLE 1

Influence of Various Additives on the Rate of Ethyl Pyruvate Hydrogenation

Additive[a]	Conversion[b] (%)		Initial rate (mmol g^{-1} h^{-1})	
	AcOH	Toluene	AcOH	Toluene
Unmodified reaction	50	45	121	200
	100	100	960	1600
	20	50	66	158
	22	54	83	188
	31	47	109	226
	31	47	102	167

[a] Additive concentration 0.21 m*M*.
[b] After 2 h.

compared to the unmodified reaction. No or only minor (13%) rate enhancements were observed upon addition of substituted naphthalene compounds, which are structurally similar to the anchoring part of PNE. An increase in concentration of the additives by a factor of 10^3 had no significant influence on the hydrogenation rate. These results indicate that only PNE can induce rate acceleration, whereas additives containing only one of the characteristic structural elements of PNE, either a naphthalene or a pyrrolidine ring, are inefficient. It should be mentioned that no enantiodifferentiation (ee = 0) was observed in the presence of (*R*)-(+)-1-(2-naphthyl)ethanol.

DISCUSSION

Cinchonidine and PNE: Structural Comparison

In earlier studies of the enantioselective hydrogenation of α-ketoesters, only cinchona alkaloids and some hydrogenated and O-methylated derivatives proved to be efficient (2, 18). We have shown recently (21) that structurally simple chiral amino alcohols can also induce considerable enantiodifferentiation in this reaction. At present, the most promising synthetic modifier is (*R*)-2-(1-pyrrolidinyl)-1-(1-naphtyl)ethanol. As shown in Schemes 2 and 3, there are similarities between cinchonidine, the most efficient cinchona alkaloid from a natural source, and PNE. Both of them can be characterised by three important functional parts: (i) the aromatic ring system (adsorption on the metal surface), (ii) stereogenic center(s) (enantiodifferentiation), and (iii) basic amine function (interaction with the reactant). Earlier results (15, 16) and the synthesis of several new modifiers (21) have proved that an efficient modifier of Pt for α-ketoester hydrogenation should possess these moieties.

In PNE a naphthalene ring serves as the anchoring part, whereas a quinoline ring is characteristic of cinchona alkaloids. A modifier similar to PNE, but possessing a quinoline anchoring moiety, viz., (*R*)-2-(1-pyrrolidinyl)-1-(4-quinolyl)ethanol, gave ee's similar to those of PNE (48–66 and 68–46%, respectively, under identical conditions) (21). These experimental observations indicate that the N heteroatom in the quinoline ring has no primary importance in the adsorption process. Consequently, it is very unlikely that cinchonidine would adsorb perpendicular to the Pt surface via the quinoline N atom assigning a crucial role to the heteroatom in the adsorption of the modifier, as has been proposed recently (8). However, this experimental evidence supports another suggestion, that the aromatic anchoring moiety adsorbs horizontally on a flat Pt surface, and its strong adsorption immobilizes the modifier–reactant complex and favours enantiodifferentiation (4, 7, 10). This concept is in accordance with literature data (30, 31), according to which naphthalene adsorbs horizontally on a flat Pt surface.

Cinchona alkaloids contain five stereogenic centers (C-3, C-4, C-8, C-9, and N-1; see Scheme 2). Cinchonidine and cinchonine, differing in C-8 and C-9 configuration, afford products of opposite configuration (17). This shows that only C-8 and C-9 can be important in determining the configuration of the enantiomer produced in excess. The replacement of the OH group with hydrogen removes the stereogenic center at C-9, but this cinchonidine derivative still induces some enantiomeric excess (44% ee) (15). It seems that it is the stereogenic center of cinchonidine at C-8 which is of crucial importance in the hydrogenation of α-ketoesters. In the much simpler molecule of PNE there is only one stereogenic center (C-7; see Scheme 3), which is in a position analogous to C-9 in cinchonidine and sufficient for obtaining higher than 70% ee.

The basic N-1 function, which is assumed to be responsible for "docking" to the reactant, is incorporated in a rather rigid quinuclidine framework in cinchonidine and

in a conformationally more flexible pyrrolidine ring in PNE (Schemes 2 and 3). The 1,4-arrangement of the N-1 and O atoms is similar in both cases. Other synthesised 2-aminoethanol derivatives possessing a secondary N-1 atom or a tertiary N-1 with two simple alkyl substituents provided ee lower than PNE (21). It seems that incorporation of N-1 into a pyrrolidine ring is advantageous for obtaining high ee.

Reaction Kinetics and Enantiodifferentiation

Kinetic studies of the enantioselective hydrogenation of ethyl pyruvate on Pt/alumina modified with PNE have shown that the efficiency of this new synthetic modifier is comparable to that of cinchonidine. In many respects Pt/alumina modified by each of the two modifiers behaves similarly. This is the case, e.g., for the influence of solvents (1, 26, 32, 33). With both systems, the highest ee was obtained in acetic acid. The influence of protonation of N-1 on the enantiodifferentiation and reaction rate has been discussed elsewhere (9, 26). The use of nonpolar solvents (e.g., toluene) is also advantageous for both reaction rate and ee (Fig. 4). An increase in solvent polarity in the range E_T^N = 0–0.5 diminishes the initial rate and enantioselectivity. One- and two-dimensional NMR analyses, combined with semiempirical molecular orbital calculations (34, 35), showed that the solvents influence the conformation of cinchona alkaloids and their derivatives. For example, methoxyquinidine adopts an "open" conformation (N-1 points away from the quinoline ring) in $CDCl_3$, but prefers a "closed" conformation (N-1 points towards the quinoline ring) in CD_2Cl_2. Though it is not possible yet to determine the orientation of the modifier adsorbed on Pt, we propose that the conformational changes due to solute–modifier interaction represent an important component of the influence of apolar and moderately polar solvents on initial rate and ee. In the range of higher polarity ($E_T^N > 0.5$) the solvent effect cannot be generalised due to special interactions between solvent and reactant or modifier, as pointed out under Results.

The reaction temperature is one of the most influential parameters of α-ketoester hydrogenation. In this respect, Pt modified by either cinchonidine or PNE behaves similarly; high ee is achieved at room temperature or below (7, 11, 32). No unambiguous interpretation of this behaviour has yet been published. Our kinetic study (Figs. 5 and 6) and NMR analysis indicate that the loss of enantioselectivity of the PNE-modified Pt/alumina at temperatures higher than 20–25°C is mainly due to the partial hydrogenation of the unsubstituted naphthalene ring. The resulting (5,6,7,8)-tetrahydronaphthalene derivative induces only moderate enantioselectivity, which is attributed to the weaker "attachment" of the half-hydrogenated naphthalene ring to the Pt surface. This explanation is based on our former observation that a modifier similar to PNE but possessing only a benzene ring instead of the α-naphthyl moiety ((*R*)-2-(1-pyrrolidinyl)-1-phenylethanol) yielded only negligible ee (21).

The partial hydrogenation of PNE explains not only the unusually strong effect of temperature on ee and initial rate, but also the influence of pressure and catalyst loading (Figs. 1 and 7). Generally, we can conclude that severe reaction conditions or high hydrogen concentration on the Pt surface are unfavourable and diminish the enantioselectivity of the PNE/Pt system.

For comparison, a great variety of partially hydrogenated cinchonidine derivatives were found a few minutes after the hydrogenation of ethyl pyruvate over cinchonidine-modified Pt was begun (36). The interpretation of the phenomena in this system is further complicated by the fact that 10,11-dihydrocinchonidine, e.g., provides higher ee than cinchonidine itself, whereas the partial hydrogenation of the quinoline moiety diminishes the enantioselectivity (15). Interestingly, an increase in hydrogen pressure from 10 to 75–100 bar improves ee in this system (11), an effect which has not yet been explained. We propose that the improvement of ee at higher pressures is connected with the presence of the quinoline ring in the modifier. We have found recently (21) that on substituting the naphthalene moiety of PNE by quinoline, ee increased from 48 to 66% with increasing hydrogen pressure from 1 to 75 bar, in contrast to the decrease from 68 to 46% observed with PNE.

The extent of rate acceleration (by a factor of 7–8) observed in the presence of PNE is in the range found with cinchonidine (15, 16, 32). It has been proposed (16) that this characteristic rate acceleration with cinchonidine is partly due to its action as an alicyclic N base (N-1 atom) and its effect as an aromatic adsorbate (quinoline moiety) on the apparent specific activity of platinum. In contrast, our results shown in Table 1 clearly demonstrate that PNE influences the reaction only as a whole molecule ("ligand-accelerated" reaction (29)). The various additives, which represent solely the basic pyrrolidine part or the aromatic moiety of PNE, had no positive influence on the initial rate or conversion.

Interestingly, the basicity of *N*-methylpyrrolidine in aqueous medium (pK_a = 10.46) is about the same as that of quinuclidine N-1 in cinchonidine (pK_a = 10.01) (37, 38). A possible explanation of the contradictory effect of tertiary N bases on the initial rate of pyruvate hydrogenation is the complex effect of solvents. The highest rate acceleration (by a factor of 2.4–6.5) was observed in ethanol (16). A minor positive effect in the low concentration range was obtained in toluene (6). In acetic acid we could not detect any rate enhancement by the addition of cyclic tertiary amines, as illustrated in Table 1.

The efficiency of PNE as chiral modifier is shown by the

low modifier : converted reactant molar ratio 1 : 30,000. At this ratio the PNE/Pt system shows maximum performance (reaction rate and ee) in acetic acid. In the case of cinchonidine-modified Pt, the generally applied ratios are around 1 : 1000 (6, 33, 39). Using 10,11-dihydro-*O*-methylcinchonidine, the best known modifier of the reaction in acetic acid as a solvent, it was possible to increase this ratio to 1 : 130,000 without losing selectivity (6).

Summarising our results, we can state that the development of the new, simple, and efficient modifier PNE provides new opportunities, broadening the scope of the Pt-catalysed enantioselective hydrogenation of α-ketoesters. For the first time, substantial enantiomeric excesses have been obtained with modifiers other than the traditional cinchona alkaloids. In contrast to cinchona-type modifiers, the different structural elements of PNE can be readily altered. This facilitates systematic studies of structure–activity and structure–selectivity relationships (21, 22) and should provide new insights into the mechanism of enantioselection. We are confident that further work will lead to more efficient modifiers with a wider application range and, eventually, to new catalyst systems for other classes of enantioselective transformations.

ACKNOWLEDGMENT

Financial support from the Swiss National Science Foundation (Program CHiral 2) is gratefully acknowledged.

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