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Design of New Modifiers for the Enantioselective Hydrogenation of Ethyl Pyruvate

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All efficient chiral modifiers for Pt in the enantioselective hydrogenation of α-ketoesters possess a basic, secondary or tertiary N atom for interacting with the carbonyl group of the reactant and an aromatic ring system for adsorptive anchoring of the activated complex on Pt. Analysis of the available data suggested that an enlargement of the naphthalene or quinoline anchoring moiety should improve the enantioselection. Accordingly, 1-(9-anthracenyl)-2-(1-pyrrolidinyl)ethanol (10) has been synthesized and tested in the hydrogenation of ethyl pyruvate. The best enantiomeric excess achieved with the new modifier was 87%, which is 12% higher than the optimized value obtained with the corresponding naphthalene derivative (4). A further advantage of the new modifier is the higher stability against self-hydrogenation. Hydrogenation of ethyl pyruvate in the presence of modifier mixtures indicated the following order of adsorption strength on Pt: cinchonidine > 10 > 4. This ranking correlates with the best enantiomeric excesses obtained with these modifiers. Compared with the other modifiers, the number of possible conformations for 10 is reduced because of the symmetry of the anthracenyl ring system. Molecular mechanics calculations suggest that the energy and geometry of the transition complexes between ethyl pyruvate and 10 or 4 are similar. Accordingly, the better efficiency of 10 should be due to its stronger adsorption on Pt and higher acceleration of the modified reaction compared with the competing nonenantioselective (unmodified) reaction. Substituting the 9-anthracenyl group of 10 with a 9-triptycenyl moiety led to a complete loss of enantiodifferentiation, demonstrating that the extended *flat* aromatic ring system is a crucial structural element of efficient modifiers for α-ketoester hydrogenation.

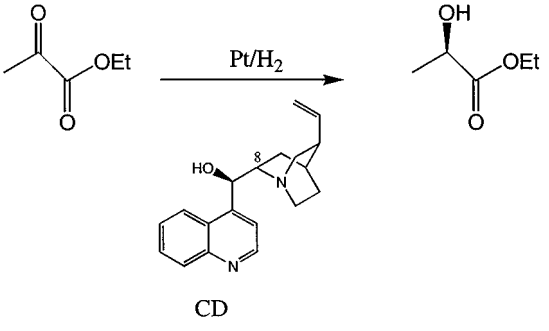
INTRODUCTION

The enantioselective hydrogenation of α-ketoesters over cinchona-modified Pt, discovered by Orito *et al.* (1), has gained great attention (2–4). An attractive feature of the reaction is that there is no need for a troublesome (and expensive) pretreatment to provide the chiral information to the metal surface. It is sufficient to add traces of the chiral modifier [a few hundred ppm relative to the reactant (5, 6)] to induce impressive changes in the product distribution.

The most studied reaction, the transformation of methyl pyruvate or ethyl pyruvate (EP) to the corresponding lactate, is shown in Scheme 1. Strong efforts have been made to understand the role of the chiral modifier and to find new efficient substitutes for the cinchona alkaloids. Three distinctly different research strategies have been applied. At first, several chiral compounds with natural origin were tested in a purely empirical way and with limited success. Codeine, strychnine, and brucine (7) provided only 2–12% enantiomeric excess (ee). Another alkaloid, dihydrovinpocetin (8), afforded 30% ee, which is still well below the 90–92% achievable with cinchonidine (CD) or 10,11-dihydrocinchonidine (9).

The other two directions, the structural modification of CD (10, 11) and the synthesis of some simple chiral amino alcohols and amino esters (12–15), provided important information on the role of various structural parts of the modifier, which will be summarized briefly, because it constitutes the basis for the rational design pursued in this work.

It was early established (11) that, besides the crucial stereogenic center at C-8, CD possesses two important structural parts (Scheme 1): the quinuclidine N atom for interaction with the pyruvate molecule ("docking" moiety)



CD

SCHEME 1

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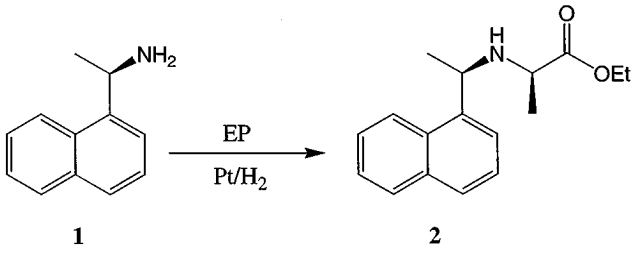


1 2

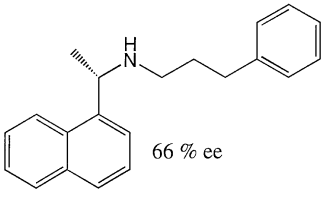
SCHEME 2

and the aromatic ring system for adsorption on Pt ("anchoring" moiety).

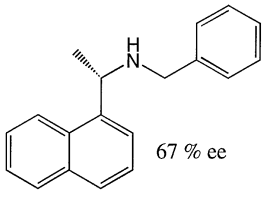
With respect to the chemical nature of the docking moiety, all the efficient modifiers contain a secondary or tertiary N atom in α or β position to the stereogenic center. Primary amines are not stable under the reaction conditions and are rapidly alkylated by EP (condensation of the amino group with the activated carbonyl group of EP followed by reduction of the imine). An example is the transformation of naphthylethylamine **1** to **2** (Scheme 2), which acts as an efficient modifier affording 82% ee under optimized conditions (15–17).

It has been proposed (18) that the quinuclidine N stabilizes the half-hydrogenated state of EP by a N–H–O-type interaction. This proposal is in line with recent molecular modeling studies (19, 20). Similarly, theoretical calculations (21, 22) suggested that in protic polar solvents the protonated quinuclidine N atom of CD interacts with the carbonyl O atom of EP by H bonding, providing again a N–H–O-type interaction.

The O–C–C–N structural part is characteristic of cinchona alkaloids (Scheme 1) and other 1,2-amino alcohol-type chiral auxiliaries. An important role in enantiodifferentiation was attributed earlier also to the O atom (3, 11). However, there are several efficient modifiers of EP hydrogenation that possess no O atom at all. Two of these compounds, prepared by reductive alkylation of **1**, are shown in Scheme 3, together with the ee values achieved (15). These examples indicate that it is the basic N that is responsible for the reactant–modifier interaction, though the adjacent OH group present in other modifiers can be advantageous.



66 % ee



67 % ee

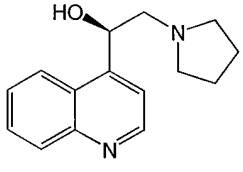
(Pt/alumina, AcOH, optimized conditions)

SCHEME 3

A crucial question is the adsorption of the modifier on Pt. H/D exchange experiments indicated that the quinoline rings of CD adsorb parallel to the Pt surface, while the quinuclidine part of the modifier is not in direct contact with Pt (23). On the contrary, a perpendicular adsorption of the quinoline rings via the N atom was proposed on the basis of "single turnover" studies (3). However, this proposal is not in line with catalytic results obtained with the modifiers **3** and **4** shown in Scheme 4, which differ only in the anchoring moiety. At low pressure (1–10 bar) they provide similar ee's for (*R*)-lactate under otherwise identical conditions (12). This is an indication that the extended aromatic π-electron system is important in the adsorption process, whereas the quinoline N atom seems to have little influence. Note that the adsorption of naphthalene parallel to the Pt surface was evidenced by STM and other physicochemical methods (24, 25).

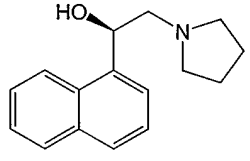
A third model has been proposed recently (26, 27), according to which CD would adsorb on Pt in a tilted position, forming a "roof" and providing a specific "shielding" effect for the pyruvate molecule. However, no evidence of this special adsorption mode has been provided yet, and it stands in contrast to the results of isotope exchange experiments mentioned above (23).

Comparison of the modifiers **3** and **4** in Scheme 4 also demonstrated that the stability against hydrogenation of the naphthalene ring system at pressures above 10 bar is considerably lower than that of the quinoline moiety (12).



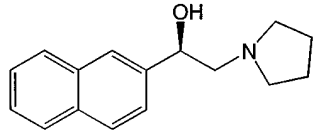
3

48 % ee (1 bar)
55 % ee (25 bar)
66 % ee (75 bar)



4

68 % ee (1 bar)
47 % ee (25 bar)

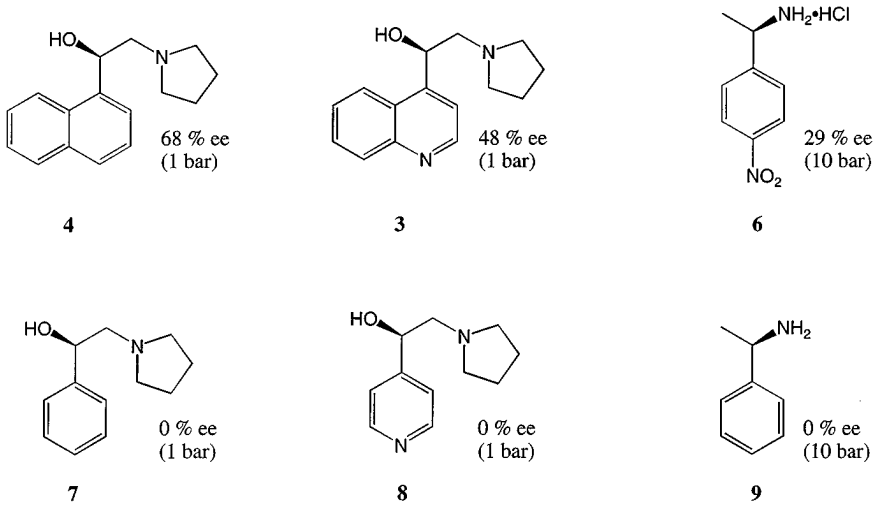


5

42 % ee (1 bar)
21 % ee (25 bar)

(Pt/alumina, AcOH)

SCHEME 4



SCHEME 5

The steric hindrance exerted by the aromatic ring system of the modifier has been shown to be important. (*R*)-2-(1-Pyrrolidinyl)-1-(1-naphthyl)ethanol (**4** in Scheme 4) afforded 75% ee under optimized conditions (14, 17). When changing the point of attachment of the pyrrolidinylethanol moiety to the naphthalene ring by one position (**5**), the excess of (*R*)-lactate dropped by 26% under otherwise identical conditions. This effect was attributed to the smaller steric hindrance for the formation of (*S*)-lactate.

The most important requirement is that the modifier should be anchored onto Pt by at least two adsorption sites [Scheme 5 (13, 16)]. This is the case when the modifier possesses a naphthalene (**4**) or quinoline (**3**) ring system or a phenyl group substituted with a strongly adsorbing functional group (**6**). [Note that **6** is only the precursor of the real modifier (15). At the beginning of the reaction the nitro group is rapidly reduced to an amino group and the aliphatic amino group is alkylated by EP, as discussed above.] When one of the adsorption sites is elimated, i.e., the modifier contains a benzene (**7**, **9**) or a pyridine (**8**) ring as anchoring moiety, the ee drops to zero under otherwise identical conditions. A feasible explanation is that in this case the modifier does not adsorb in a way that would allow the required interaction. Note that the inefficiency of modifiers **7**–**9** possessing only a single aromatic ring is further experimental evidence against the validity of the "shielding" model. According to this model the decreasing size of the aromatic ring system should result in somewhat lower, but still good enantioselectivity (27).

On the basis of the comparative experiments illustrated in Scheme 5 we assumed that a modifier, similar to compound **4**, but possessing an anthracenyl instead of the naphthyl group as anchoring moiety, could be even more efficient in enantiodifferentiation. Both enantiomers of this modifier (**10** in Scheme 6) have been synthesized and tested in the enantioselective hydrogenation of EP. In addition, **11** (Scheme 6) was also prepared which enabled us to demonstrate the role of the flat aromatic ring system in the adsorption of the modifier on Pt.

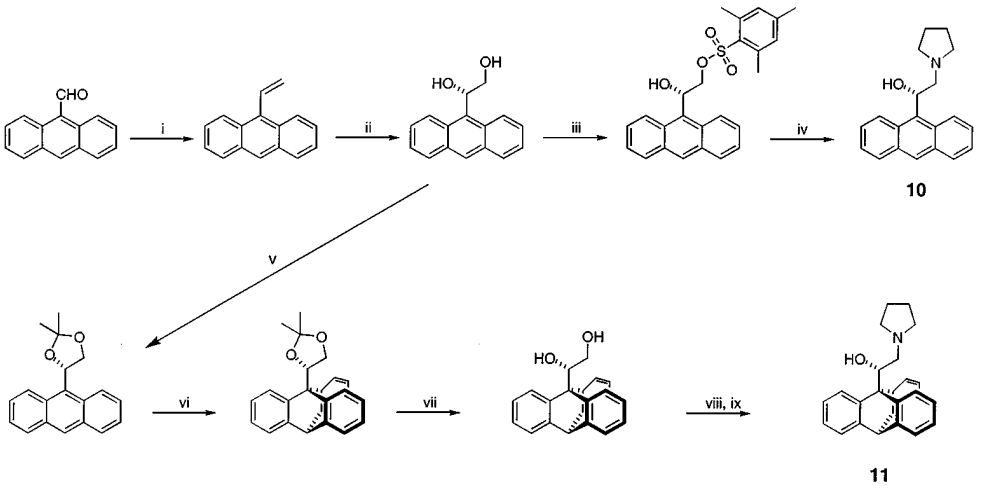
EXPERIMENTAL

In the following, the generally used abbreviations (CN, CD) are applied for the cinchona alkaloids, but for the sake of simplicity the synthetic modifiers are represented by boldface numbers as indicated in Schemes 2–6.

Synthesis of New Modifiers

The synthesis of modifiers **10** and **11** is illustrated in Scheme 6. A short summary of steps i–ix can be found below. More details of the synthesis and identification of the intermediates and products are available from the authors on request.

Step (i) (28). Phenyllithium 58.7 mmol in 37 ml cyclohexane/ether was added dropwise to a stirred suspension of 62.1 mmol methyltriphenylphosphonium bromide in 165 ml THF, at 0°C. The mixture was warmed to room temperature and stirred for 30 min. Then 11.8 g (57 mmol) anthracene-9-carbaldehyde in 42 ml THF was added dropwise at 0°C. The mixture was stirred at room temperature for 15 h, then 1 ml MeOH was added. The slurry was diluted with 100 ml petroleum ether and the supernatant solution was decanted and filtered through celite. The solids remaining in the mask were washed with three 100-ml portions of petroleum ether, and the supernatant solutions were also filtered through celite. The filtrate was concentrated *in vacuo*. Purification by flash chromatography with hexane afforded 10.3 g (81%) of 9-vinyl-anthracene as a yellow solid.



SCHEME 6

Step ii (29, 30). $K_3[Fe(CN)_6]$ (49.6 g, 150 mmol), K_2CO_3 (20.8 g, 150 mmol) (DHQ)2-PHAL (395 mg, 0.5 mmol) and $K_2OsO_2(OH)_4$ (37 mg, 0.1 mmol) in 250 ml t-butyl alcohol and 250 ml water were cooled to 0°C. 9-Vinylanthracene (10.3 g, 50 mmol) was added and the slurry stirred at 0°C for 87 h. The mixture was quenched with 76 g Na_2SO_3, warmed to room temperature, and stirred for 1 h. Extraction with EtOAc followed by flash chromatography with hexane/EtOAc (1 : 1) afforded 10.1 g (84%) of (*S*)-1-(9-anthracenyl)-1,2-ethanediol. Greater than 99.5% ee was obtained via recrystallization from CH_2Cl_2/hexane.

Step iii. Anthracenyl-ethanediol (6.5 g, 27 mmol) and NEt_3 (5.7 ml, 41 mmol) were dissolved in 500 ml CH_2Cl_2. Mesitylene sulfonyl chloride (5.9 g, 27 mmol) was added and the reaction mixture stirred at room temperature for 2 weeks. Removal of the solvent *in vacuo* followed by flash chromatography with hexane/EtOAc (2 : 1) afforded 10.0 g (88%) of (*S*)-2-hydroxy-2-(9-anthracenyl)ethyl mesitylene sulfonates as a yellow paste. $[\alpha]_D = +40$ ($c = 1.37$, $CHCl_3$).

Step iv. The product of step iii was stirred in 200 ml pyrrolidine at 40°C for 10 days. The excess amine was removed *in vacuo*. The residue was stirred in 350 ml ether and 100 ml saturated $NaHCO_3$ solution for 2 h. After separation the aqueous phase was extracted with ether, dried over K_2CO_3, and concentrated *in vacuo*. Purification by flash chromatography with EtOAc/NEt_3 (100 : 1) afforded (*S*)-1-(9-anthracenyl)-2-(1-pyrrolidinyl)ethanol (**10**) as crystals. Crystallization from hot *i*-PrOH yielded 3.6 g (52%) yellow solid. $[\alpha]_D = +8$ ($c = 1.05$, $CHCl_3$), >99.5% ee by HPLC. The (*R*)-enantiomer of **10** was prepared in an analogous manner.

Step v (31). Anthracenyl-ethanediol (930 mg, 3.9 mmol) and *p*-toluenesulfonic acid (80 mg, 0.42 mmol) in 100 ml acetone were stirred for 3 h. Removal of the solvent *in vacuo* followed by flash chromatography with hexane/EtOAc (1 : 1) afforded 967 mg (89%) (*S*)-4-(9-anthracenyl)-2,2-dimethyl-1,3-dioxolane as a yellow oil. $[\alpha]_D = -5$ ($c = 1.39$, $CHCl_3$).

Step vi (32). A solution of 490 mg (3.58 mmol) anthranilic acid in 3 ml THF was added over 3 h to a refluxing mixture of 940 mg (3.4 mmol) anthracenyl-dimethyl-dioxolane and 0.5 ml (3.8 mmol) amyl nitrite in 12 ml CH_2Cl_2. The solution was concentrated *in vacuo*. Six milliliters of *o*-xylene and 250 mg maleic anhydride were added, and the solution was refluxed for 15 min. After cooling to room temperature, 15 ml water and 20 ml CH_2Cl_2 were added. The layers were separated, and the organic phase was extracted three times with 10 ml of 12% aqueous KOH, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography with hexane/EtOAc (5 : 1) afforded 952 mg (80%) (*S*)-4-(9-triptycenyl)-2, 2-dimethyl-1,3-dioxolane. Crystallization from CH_2Cl_2/hexane yielded yellow crystals (30%). $[\alpha]_D = +45$ ($c = 0.98$, $CHCl_3$).

Step vii. A solution of 0.54 g (1.5 mmol) triptycenyl-dimethyl-dioxolane and 1.45 g (7.6 mmol) *p*-toluene-sulfonic acid in 40 ml methanol was refluxed for 6 days. Removal of the solvent *in vacuo* followed by flash chromatography with hexane/EtOAc (1 : 1) afforded 333 mg (70%) (*S*)-1-(9-triptycenyl)-1,2-ethanediol as a white solid. $[\alpha]_D = -5$ ($c = 1.09$, EtOH).

Step viii. The procedure was analogous to step iii. Purification by flash chromatography with hexane/EtOAc (3 : 1) afforded (*S*)-2-hydroxy-2-(9-triptycenyl)ethyl mesitylene sulfonates as a yellow paste (81%).

Step ix. The procedure was analogous to step iv. Purification by flash chromatography with EtOH/NEt_3 (200 : 1) followed by crystallization from hot methanol yielded (*S*)-1-(9-triptycenyl)-2-(1-pyrrolidinyl)ethanol (**11**) as pale yellow crystals (46%). $[\alpha]_{365} = +7$ ($c = 1.06$, $CHCl_3$).

Catalytic Hydrogenation

Ethyl pyruvate (EP, Aldrich) was freshly distilled *in vacuo* before each reaction. AcOH (Riedel de Haën), cinchonine (CN, Fluka, 99%), and cinchonidine (CD, Fluka, >98%) were used without further purification.

Five weight percent Pt/alumina (Engelhard 4759) was pretreated in flowing nitrogen at 400°C for 30 min, followed by a reductive treatment in 30 ml min^{-1} hydrogen for another 90 min. The catalyst was then cooled to room temperature in flowing hydrogen and transferred to the autoclave under exclusion of oxygen. The catalyst was first contacted with the solvent containing the proper amount of modifier. The metal dispersion after heat treatment was 27% as calculated from the TEM images.

The hydrogenation of EP was carried out in a 100-ml stainless-steel autoclave (Baskerville) with a 50-ml glass liner and PTFE cover. The reaction temperature was controlled by the bath in which the reactor was immersed. The mixture was stirred magnetically at 1000 rpm. The pressure was kept constant with computerized constant volume–constant pressure equipment (Büchi BPC 9901) which allowed calculation of the rate of hydrogen consumption. The (initial) reaction rate was determined between 0 and 20% conversion by linear regression. The influence of interparticle mass transport was found to be negligible, based on experiments with varying amounts of catalyst.

The enantiomeric excess was determined at full conversion with a HP 5890A gas chromatograph using a chiral WCOT Cyclodextrin-β-2,3,6-M-19 (Chrompack) capillary column. The enantioselectivity is expressed as ee (%) $= |[R] - [S]|/[R] + [S]$.

Theoretical Calculations

Molecular mechanics calculations were performed to gain some insight into the structure of the modifier–reactant complex, which is assumed to be adsorbed parallel to the platinum surface via the aromatic ring system and the carbonyl group of EP. This assumption is justified based on previous H/D isotope exchange experiments (18) and the fact that the adsorption enthalpy (33) is much higher than the hydrogen bond interaction energy which is calculated by molecular mechanics.

Calculations were carried out using the Discover Molecular Simulation Program (Version 4.0.0) from MSI with the CFF91 force field (Version 2.0) (34). The default values were used during geometry optimization except that the aromatic ring system of the modifiers and the carbonyl groups of EP were kept in one plane (restraint type: out of plain, force constant: 10,000). The calculations were repeated with the HyperChem program from Hypercube (Version 4.5) using the MM+ force field without any constrains (smallest significant difference: 0.2 kcal/mol).

RESULTS

*Comparison of 1-(9-Anthracenyl)-2-(1-pyrrolidinyl)ethanol (**10**) and 1-(1-Naphthyl)-2-(1-pyrrolidinyl)ethanol (**4**)*

Both enantiomers of the new modifier **10** have been synthesized, as described under Experimental, and tested in the hydrogenation of EP. The preliminary study on the performance of **10** indicated that the influence of reaction parameters was in many respects similar to that observed earlier when using the naphthalene derivative **4** (14). For example, reductive pretreatment of Pt/alumina at 400°C improved the ee considerably. Acetic acid was the best solvent, suggesting that protonation of the pyrrolidine N atom improves the enantiodifferentiation (21, 22).

The new modifier **10** was more efficient with respect to ee and rate acceleration ["ligand acceleration" effect (5)]. This is illustrated by the kinetic results in Figs. 1 and 2. With both modifiers, higher modifier concentration increased ee up to a concentration limit of 0.15 mmol $liter^{-1}$ (Fig. 1). This concentration corresponds to a modifier : reactant molar ratio of 1 : 30,000. Above this concentration the changes were minor and modifier **10** provided 12–13% higher ee than modifier **4** [data for **4** are taken from Ref. (13)]. In contrast to modifier **4**, no maximum of the reaction rate could be observed with modifier **10** up to a concentration of 1 mmol $liter^{-1}$ (Fig. 2). When applying the modifiers in sufficiently high concentration, a rate acceleration (rate of reaction, related to that of the unmodified reaction) up to a factor of 20–21 was observed with **10**, as compared with a factor of 7–8 induced by **4** (14).

A further advantage of **10**, as compared with the former successful synthetic modifiers **2** and **4**, is the significantly

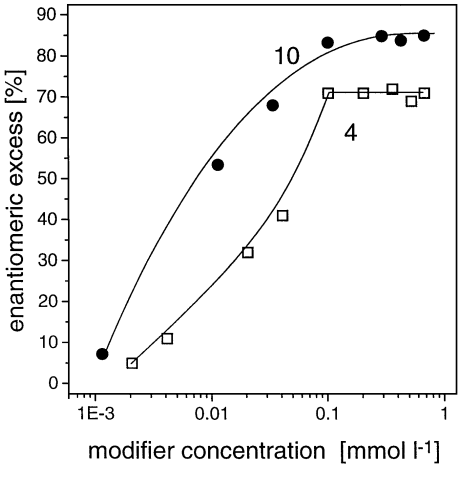


FIG. 1. Influence of modifier concentration on the enantiomeric excess of (*S*)- or (*R*)-lactate in the hydrogenation of EP over Pt/alumina modified with **10** or **4** [(*S*) or (*R*) enantiomer, respectively]. Reaction conditions for modifier **10**: 10°C, 40 mg catalyst, 10 ml AcOH, 45 mmol EP, 70 bar H_2; for modifier **4**: 25°C, 100 mg catalyst, 20 ml AcOH, 90 mmol EP, 10 bar H_2.

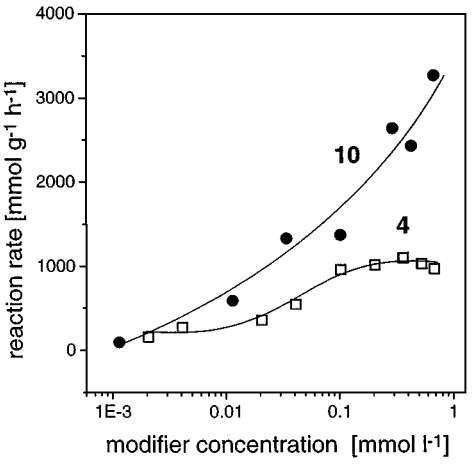


FIG. 2. Influence of modifier concentration on the initial rate of EP hydrogenation over Pt/alumina modified with **10** or **4** [(*S*) or (*R*) enantiomer, respectively]. For conditions see Fig. 1.

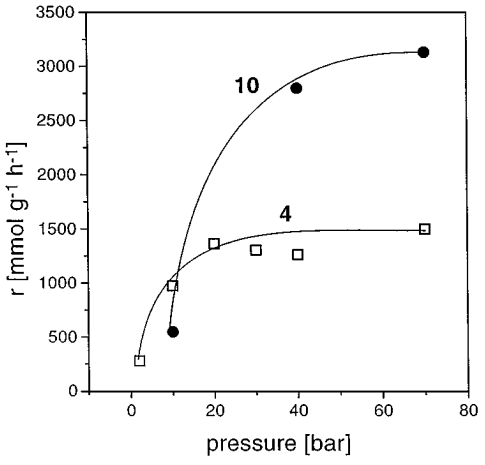


FIG. 4. Influence of hydrogen pressure on the initial rate of EP hydrogenation over Pt/alumina modified with **10** or **4** [both (*R*)-enantiomers]. For conditions see Fig. 3.

higher stability at high hydrogen pressures. This behavior is illustrated in Figs. 3 and 4. When applying **10**, the reaction rate increased with increasing pressure, expectedly, but the ee barely changed between 10 and 100 bar (not all data are shown in Figs. 3 and 4). The poor performance of modifier **4** at pressures higher than 10 bar was proved to be due to the partial hydrogenation of the naphthalene ring system, resulting in weaker adsorption on Pt (14). Note that **10** provided significantly higher ee even at 10 bar (Fig. 3), when the saturation of the naphthalene rings was found to be negligible.

The highest ee achieved with the (*R*)-enantiomer of **10** was 87% (conditions: 38 mg Pt/alumina, 3.4 mg modifier, and 5 ml EP in 10 ml AcOH were hydrogenated at 10°C and 70 bar). The (*S*)-enantiomer provided a slightly lower ee by about 2%. This difference may be due to the presence of traces of impurities and to analytical error.

Another new modifier, (*S*)-1-(9-triptycenyl)-2-(1-pyrrolidinyl)ethanol (**11**, Scheme 6), which differed from the (*S*)-conformer of **10** only in the anchoring moiety, was also synthesized. Interestingly, no enantiodifferentiation (<5% ee) could be detected in EP hydrogenation when using **11** as chiral modifier for Pt/alumina. The influence of substituting the flat aromatic anthracenyl ring system in **10** by the "three-dimensional" triptycenyl moiety in **11** is discussed later.

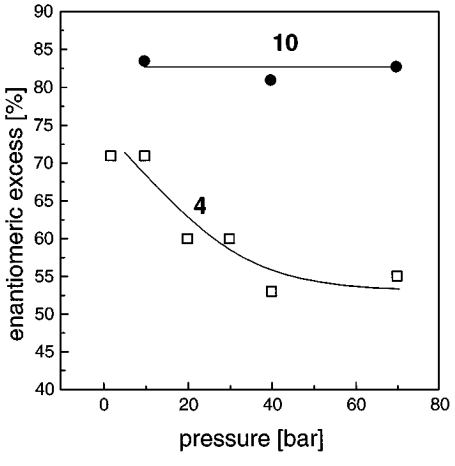


FIG. 3. Influence of hydrogen pressure on the enantiomeric excess of (*R*)-lactate in the hydrogenation of EP over Pt/alumina modified with **10** or **4** [both (*R*)-enantiomers]. Reaction conditions for modifier **10**: 10°C, 40 mg catalyst, 10 ml AcOH, 45 mmol EP, 3.4 μmol modifier; for modifier **4**: 25°C, 100 mg catalyst, 20 ml AcOH, 90 μmol EP, 6.2 μmol modifier.

*Comparison of Modifiers **10** and **4** with Cinchona Alkaloids*

The hydrogenation of EP was performed in the presence of two different modifiers to obtain some information on their relative strength of adsorption on Pt under the reaction conditions. CN was always used as one of the components, which alone provides the (*S*)-lactate in excess. The other modifier was (*R*)-**10**, (*R*)-**4**, or CD (for comparison); all three compounds provide (*R*)-lactate in excess, when used alone as the source of chiral information. The results of these experiments are shown in Figs. 5 and 6. When applying CD or CN alone, the ee values are similar. A deviation from the linear correlation between ee and molar fraction of CD in favor of (*R*)-lactate formation was found when using a mixture of the two alkaloids. This is an indication that CD adsorbs on Pt more strongly than CN and has greater influence on the direction of enantiodifferentiation over the entire composition range. Note that similar results were obtained earlier, though a strikingly different catalyst pretreatment procedure and reaction conditions were applied (35).

Deviation in favor of (*S*)-lactate formation was observed when mixing CN with either synthetic modifier **10** or **4**. Interestingly, even a CN:**4** = 1:9 mixture provided 44%

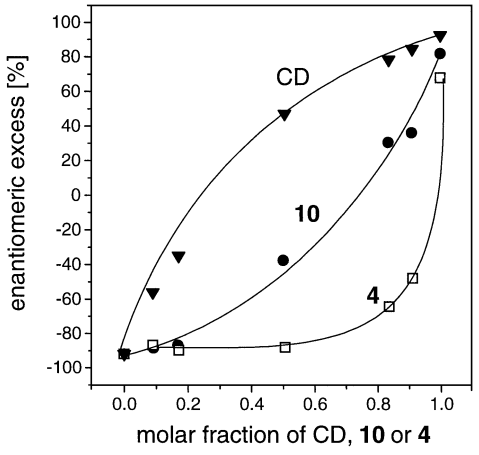


FIG. 5. Enantiomeric excess of (*R*)- or (*S*)-lactate in EP hydrogenation, when using a mixture of two modifiers [CN and one of CD, **10** (*R*) and **4** (*R*)]. Reaction conditions: 70 bar H_2, 10°C, 100 mg Pt/alumina, 20 ml AcOH, 91 mmol EP, total amount of 8 μmol modifier.

excess of (*S*)-lactate, suggesting that **4** is less strongly adsorbed than CN on the Pt surface. This behavior is due at least partly to the partial hydrogenation of the naphthalene ring system during reaction at 70 bar, as discussed above. This side effect could be eliminated when performing the experiments at 10 bar or below, but these conditions are far from the optimum for the cinchona alkaloids and the comparison would be less interesting.

There are big differences in the rate of EP hydrogenation in the presence of various modifier mixtures (Fig. 6). Both **4** and **10** decrease the reaction rate as compared with the rate achieved with CN alone. Adversely, CD and CN–CD mixtures provide higher rates than CN alone.

Theoretical Calculations

As in previous computational studies of the structure of the diastereomeric transition states, we assumed that the aromatic rings of the modifier and the carbonyl groups of EP are adsorbed parallel to a flat (ideal) Pt surface (23, 25, 36–38). The structure of the transition complex is assumed to resemble the transition state and enantiodifferentiation occurs due to energetical favoring of one of the diasteromeric complexes. In contrast to the previous calculations (21, 22), the simulation of the flat adsorption is achieved by keeping the aromatic rings of **4** and **10** and the carbonyl groups of EP in a plane during energy minimization of the modifier–EP complex. For both modifiers the protonated forms were used for calculations. The calculated geometries, illustrated in Scheme 7, are very similar for modifiers **4** and **10**. In both cases the formation of (*R*)-lactate is favored, when using the (*R*)-conformers of the modifiers, though the energy differences between the complexes leading to (*R*)- or (*S*)-lactate formation are rather small (around 0.35 kcal mol^{-1}). For comparison, similar calculations have been performed with the Hyperchem program (MM+ force field), which provided almost the same optimized geometries, but considerably higher energy differences in favor of (*R*)-lactate formation (2–4 kcal mol^{-1}). This comparative study shows that although the absolute values of the calculated energies may differ depending on the software used, the direction of enantiodifferentiation is clearly indicated.

Independent of the size of the energy differences between the modifier–EP transition complexes (Scheme 7), the almost identical values suggest that the higher ee achieved with **10** (as compared with **4**) cannot be due to an energetically more favored interaction with EP or some extra steric hindrance between **10** and EP.

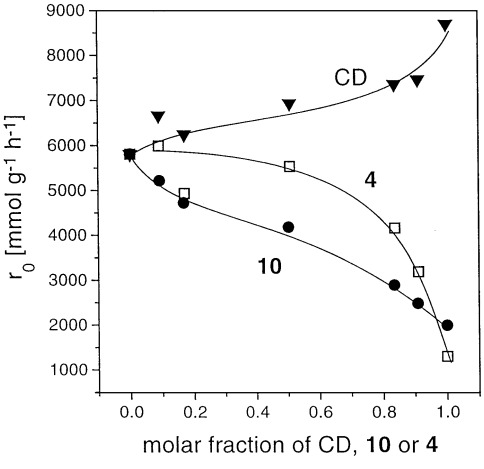
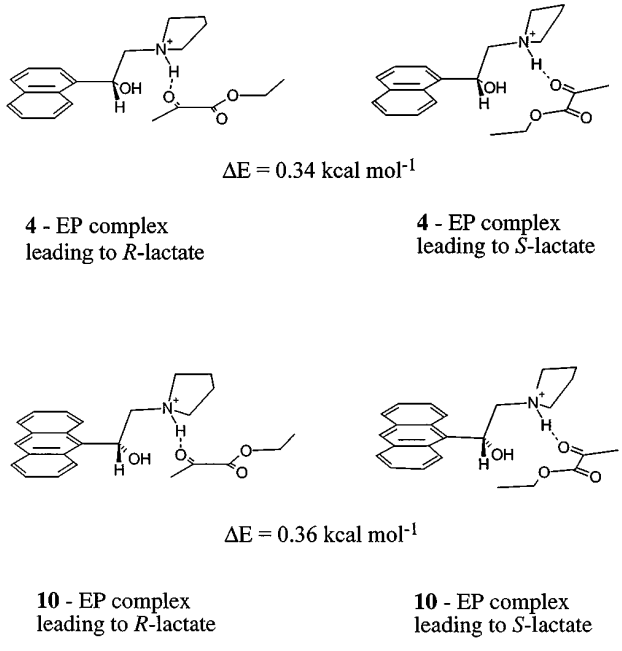
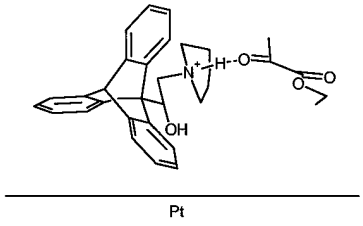


FIG. 6. Reaction rate in EP hydrogenation, when using a mixture of two modifiers [CN and one of CD, **10** (*R*) and **4** (*R*)]. For conditions see Fig. 5.



SCHEME 7



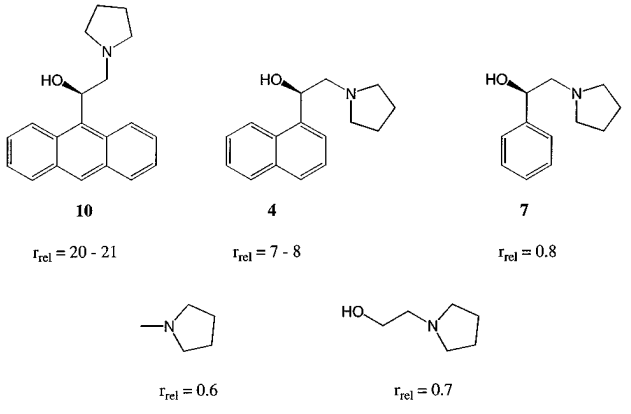
SCHEME 8

Molecular modeling provided a likely explanation of the inefficiency of modifier **11**. The minimum energy conformation of **11** could not be positioned in any feasible way onto a flat Pt surface. This is an indication that the absence of enantiodifferentiation with **11** is due to the "propeller-like" structure of the aromatic ring system, which hinders the π bonding interaction with the surface Pt atoms (Scheme 8).

DISCUSSION

Let us consider first the rate acceleration, i.e., the higher rate observed in the presence of chiral modifier as compared with the rate of the unmodified (racemic) reaction. It was proposed earlier (18) that the rate acceleration is due to the stabilization of the half-hydrogenated state of EP by CD. The importance of this interaction in apolar medium has also been emphasized recently by theoretical calculations (20). It has also been shown by molecular modeling (21) that in acetic acid (i) there is an interaction already between the protonated form of CD and EP (i.e., before the half-hydrogenated form is produced), and (ii) the CD–EP complex resembles the half-hydrogenated state of the pyruvate molecule.

The N–H–O-type interaction between the basic N atom of the modifier and the carbonyl O atom of pyruvate is an important but not sufficient requirement for achieving rate acceleration (and enantiodifferentiation). This is illustrated by the data in Scheme 9, based on the present work and former results (14). When applying *N*-methyl-pyrrolidine or pyrrolidinyl-ethanol, the rate of EP hydrogenation related to the rate of unmodified reaction under similar conditions in AcOH (r_{rel}) is less than unit. Both compounds can interact via the basic N atom with the carbonyl O atom of EP; however, this interaction does not result in rate acceleration. Only those compounds (**10** and **4**) that can properly anchor the N base–EP adduct onto the Pt surface, are able to increase the reaction rate. This indicates that the origin of rate acceleration is the same as that of enantiodifferentiation: an N–H–O-type interaction between reactant and modifier, *both adsorbed appropriately* on the Pt surface. The positive correlation between rate acceleration and ee is also illustrated by the comparative studies in Figs. 1–6.



SCHEME 9

The catalytic test of modifier **10** demonstrated that substitution of the naphthalene ring system of the already efficient modifier **4** with an anthracenyl anchoring moiety improved the ee significantly. The better performance of **10** compared with **4** could be explained by a change in the modifier–EP interaction and/or in the adsorption of the modifier–EP adduct. The former possibility seems unlikely based on molecular modeling. The calculations strongly suggested that there is no significant deviation in the interaction energies or any extra steric hindrance against the formation of (*R*)- or (*S*)-lactate, when applying modifier **10** instead of **4**.

With respect to the interaction of Pt with the modifier–EP complex, the hydrogenation of EP in the presence of modifier mixtures indicated that **10** adsorbs more strongly than **4** on Pt. The difference at high hydrogen pressure is due partly to the higher stability of the anthracenyl moiety against hydrogenation (16).

The comparative catalytic experiments showed that the strength of adsorption and the observed rate acceleration are strongly correlated features of the modifiers. According to a former simple kinetic model (39), lactate is formed from pyruvate via a modified enantioselective route and an unmodified route leading to racemic product. The measured overall rate is the sum of the rates of modified and unmodified reactions. The ee can be improved by increasing the rate of the modified reaction (resulting in higher overall rate, i.e., rate acceleration) or by suppressing the unmodified reaction. The latter is also likely in the case of **10** due to the larger site requirement of the anthracenyl moiety, compared with the naphthyl group of **4**.

CONCLUSIONS

In recent years we have focused on the development of new, structurally simple chiral amines as modifiers for Pt in the enantioselective hydrogenation of α-ketoesters. An efficient member of this family is 1-(1-naphthyl)-2-(1-pyrrolidinyl)ethanol (**4**), which afforded 75% ee at low pressures (1–10 bar) (14). Based on the influence of

structural modifications on the efficiency of these new synthetic modifiers, we predicted that the enlargement of the anchoring moiety should improve ee, on the condition that the aromatic ring system still possesses a flat, two-dimensional structure. Synthesis and catalytic testing of 1-(9-anthracenyl)-2-(1-pyrrolidinyl)ethanol (**10**) and 1-(9-triptycenyl)-2-(1-pyrrolidinyl)ethanol (**11**) confirmed our assumption. When comparing the best ee values achieved, modifier **10** was found to be almost as efficient as the cinchona alkaloids. Moreover, the studies of several structurally simple chiral amino alcohols and amino esters (12, 15) provided new insights concerning the reactant–modifier–metal surface interaction. This knowledge may serve as a guide in the search for modifiers for other enantioselective hydrogenation reactions over Pt.

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