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# Enantioselective Hydrogenation of Ethyl Pyruvate over Pt/Alumina Modified by (*R*)-1-(1-Naphthyl)ethylamine Derivatives

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**A new chiral modifier, (*R*)-1-(1-naphthyl)ethylamine, has been tested in the enantioselective hydrogenation of ethyl pyruvate to ethyl lactate over 5 wt% $Pt/Al_2O_3$. The influence of catalyst (2–28 g liter$^{-1}$) and modifier concentration (0–20 m*M*), temperature (282–333 K), pressure (1–75 bar), and solvents was studied in a slurry reactor. The 82% enantiomeric excess (ee) at full conversion was achieved in acetic acid after optimizing the reaction parameters. Under mild conditions the new modifier affords ee's better than that achieved with cinchona alkaloids. A drop in ee at pressures higher than 10 bar and temperatures above 288 K is attributed to partial hydrogenation of the naphthalene ring, which hinders the adsorption of the modifier parallel to a flat Pt surface. Maximum rate acceleration by a factor of 12, compared to the racemic reaction, was observed after thermal treatment of the catalyst in flowing hydrogen at 673 K, followed by aerobic treatment at 273–298 K in acetic acid. It is shown that naphthylethylamine is only a precursor of the actual modifier, which is a secondary amine formed *in situ* from naphthylethylamine and ethyl pyruvate by condensation to the corresponding imine and subsequent reduction of the C=N bond. Several other derivatives of naphthylethylamine were prepared by reductive alkylation and tested as modifiers. The results indicate that the presence of an oxygen function such as a hydroxy or methoxy group, as in previously used modifiers, is not an indispensable requirement for obtaining high ee in the hydrogenation of α-ketoesters.** 

## INTRODUCTION

Various chiral amino-alcohol-type modifiers of natural origin have been tested in the enantioselective hydrogenation of α-ketoesters to the corresponding α-hydroxyesters (1–3). The most studied reaction is the hydrogenation of ethyl pyruvate (EP) to (*R*)-ethyl lactate (Scheme 1) over supported platinum catalysts (4–6). Cinchonidine and two of its derivatives (**1a**–**1c**, Scheme 1) provided enantiomeric excesses (ee) up to 95% in acetic acid at 100 bar (6). Further modifications of cinchonidine, such as alkylation of the quinuclidine nitrogen, partial hydrogenation of the quinoline ring, or acylation of the OH group resulted in a substantial decrease or a complete loss of enantiodifferentiation (7). Other members of the cinchona family (cinchonine, quinidine, quinine) (1) as well as various other nitrogen compounds of natural origin (ephedrine, strychnine, proline, codeine) were found to be less effective or hardly effective at all (3, 8, 9).

The use of cinchonidine derivatives revealed the following crucial structural elements of modifiers **1a**–**1c** (7, 10–12):

(i) A flat aromatic (quinoline) ring system is necessary for the adsorption at the surface $Pt^0$ sites ("anchoring" moiety).

(ii) The tertiary quinuclidine nitrogen is essential for the interaction with the organic reactant.

(iii) The stereogenic centers at C-8 and C-9 are responsible for the asymmetric induction. A further conclusion was that the N-1–C-8–C-9–O structural unit is important for enantioselection, but this will be disputed in this paper.

Instead of modifying the structure of the cinchona alkaloids, we recently synthesized various structurally simple amino-alcohols possessing the crucial structural elements mentioned above (13, 14). These studies led to a new efficient modifier, (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (**2**, Scheme 1), which induces enantiomeric excesses of up to 75% in the hydrogenation of EP (13, 15). The structure of **2** can be easily modified in a variety of ways. This facilitates a systematic study of the platinum–modifier–reactant interaction and the mechanism of enantioselection.

On the basis of these results, various commercially available nitrogen-containing chiral compounds were tested as modifiers for the asymmetric hydrogenation of EP (16). Preliminary screening showed that a great variety of aromatic and heteroaromatic ring systems can function as anchoring moiety of the modifier. Moreover, not only tertiary nitrogen compounds, but also primary amines and isocyanates afforded 29–67% ee in the hydrogenation of EP. A simple aromatic amine, (*R*)-1-(1-naphthyl)ethylamine (**3**, Scheme 1) was found to be the most effective modifier.

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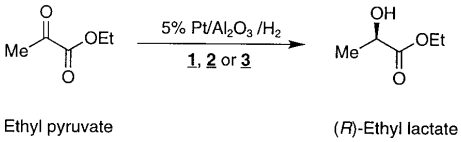
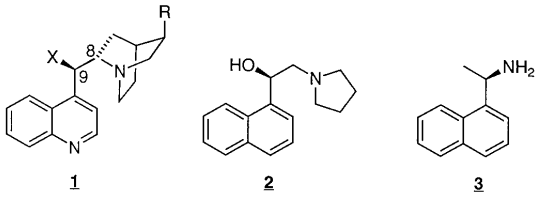



Ethyl pyruvate (*R*)-Ethyl lactate




1 2 3

**1a**: Cinchonidine (X=OH, R=$C_2H_3$)
**1b**: 10,11-Dihydrocinchonidine (X=OH, R=$C_2H_5$)
**1c**: 10,11-Dihydro-O-methylcinchonidine (X=$OCH_3$, R=$C_2H_5$)

**SCHEME 1**

Enantioselectivities up to 67% and a rate acceleration by a factor of 6, compared to the unmodified reaction, were observed in acetic acid on Pt/alumina without optimization. In other solvents, such as ethanol or toluene, enantioselectivities were moderate or low.

Here we present a detailed analysis of the hydrogenation of EP over Pt/alumina modified with **3**. In addition, various derivatives of **3** were prepared and tested as modifiers.

## EXPERIMENTAL

### *Synthesis of Modifiers*

*General.* All solvents were distilled before use. The reactions were carried out under argon atmosphere using dried glassware. Flash column chromatography used silica gel C 560, 35–70 $\mu$m, Chemische Fabrik Uetikon, and TLC used silica gel 60, Merck, 0.25 mm. Specific rotations were measured on a Perkin Elmer 241 polarimeter at room temperature, with estimated error $\pm 5\%$.

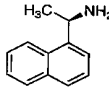
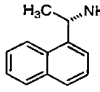
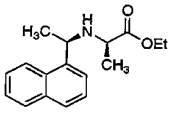
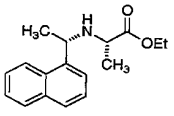
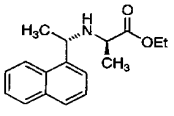
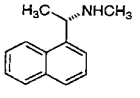
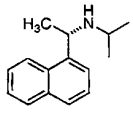
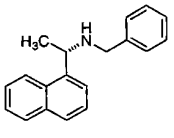
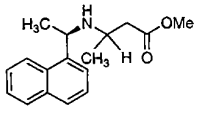
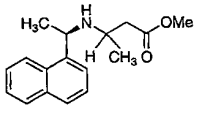
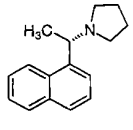
Synthesized modifiers are designated with numbers and their corresponding formulae are summarized in Table 1. Analytical data of the synthesized materials are available from the authors on request.

The methods used for the synthesis of the modifiers are described here.

*Method A.* A mixture of 5.8 mg (34 $\mu$mol) of (*S*)-1-(1-naphthyl)ethylamine **4**, 50 mg of 5 wt% Pt/alumina catalyst, and 1.2 g (10.3 mmol) of EP in 2 ml acetic acid was stirred at 25 bar $H_2$ for 1 h. After filtration, the solvent was removed by distillation (100°C, 20 mbar). The residue was dissolved in ether, $K_2CO_3$ was added, and the mixture was stirred for 1 h. Filtration, removal of the solvent *in vacuo* followed by flash chromatography with hexane/EtOAc (5:1) afforded 3.7 mg (40%) of (2*S*, 1′*S*)-*N*-[1′-(1-naphthyl)ethyl]-2-amino propionic acid ethyl

**TABLE 1**

**A Comparison of Chiral Modifiers in the Enantioselective Hydrogenation of Ethyl Pyruvate (Acetic Acid, Room Temperature, 1h Reaction Time, Reactant : Catalyst = 106 Weight Ratio, Reactant : Modifier = 1500 Molar Ratio)**

| | Modifier | Pressure (bar) | Conversion (%) | ee (%) |
|---|---|---|---|---|
| **3** |  | 75–72<br>25–22 | 48<br>54 | 51 (*R*)<br>55 (*R*) |
| **4** |  | 75–72<br>25–22 | 52<br>59 | 53 (*S*)<br>58 (*S*) |
| **5** |  | 25–21 | 83 | 55 (*R*) |
| **6** |  | 75–72<br>25–22 | 70<br>68 | 54 (*S*)<br>58 (*S*) |
| **7** |  | 75–72<br>25–21 | 62<br>78 | 51 (*S*)<br>58 (*S*) |
| **8** |  | 75–71<br>25–22 | 75<br>60 | 39 (*S*)<br>40 (*S*) |
| **9** |  | 75–73<br>25–23 | 41<br>39 | 23 (*S*)<br>36 (*S*) |
| **10** |  | 75–73<br>25–22 | 33<br>47 | 34 (*S*)<br>45 (*S*) |
| **11a** |  | 75–73<br>25–23 | 45<br>38 | 40 (*R*)<br>37 (*R*) |
| **11b** |  | 75–73<br>25–23 | 32<br>48 | 31 (*R*)<br>49 (*R*) |
| **12** |  | 75–74<br>25–22 | 19<br>53[a] | 19 (*S*)<br>9 (*S*) |

[a] Reaction time, 3 h.

ester **6**. Method A was also used for the preparation of (*S*)-*N*-benzyl-1-(1-naphthyl)ethylamine **10** (yellow oil, 34% yield) and (1′*R*)-*N*-[1′-(1-naphthyl)ethyl]-3-amino butyric acid methyl ester **11** (diastereomer **11a** as yellow oil, 131.6 mg, 28% yield; diastereomer **11b** as yellow oil, 30.0 mg, 6% yield).

*Method B (17).* A mixture of 617 $\mu$l (5.57 mmol) of EP, 954 mg (5.57 mmol) of amine **4**, and 1.68 g (7.35 mmol) of titanium (IV) ethoxide was stirred at room temperature for 1 h. The viscous solution was diluted with 5.5 ml ethanol. Sodium cyanoborohydride (274 mg, 3.7 mmol) was added, and the red solution was stirred for 16 h. After the addition of 1.1 ml water, the resulting precipitate was filtered and washed with ethanol. The filtrate was concentrated *in vacuo*, dissolved in ethyl acetate, filtered to remove the remaining inorganic solids, and concentrated *in vacuo* again. The two diastereomers **6** and **7** were separated by flash chromatography (hexane/EtOAc 5 : 1). Each diastereomer was rechromatographed with $CH_2Cl_2$ as eluent. (2*S*,1′*S*)-*N*-[1′-(1-naphthyl)ethyl]-2-amino propionic acid ethyl ester **6** was obtained as pale yellow oil (387 mg, 26% yield); (2*R*, 1′*S*)-*N*-[1′-(1-naphthyl)ethyl]-2-amino propionic acid ethyl ester **7** as yellow oil (324 mg, 22% yield).

The absolute configuration of the newly formed stereogenic center was determined by GC analysis of the corresponding *N*-Boc-alanine derivative. A mixture of 68.4 mg (0.4 mmol) of (*S*)-1-(1-naphthyl)ethylamine **4**, 100 mg of 5 wt% Pt/alumina catalyst, and 1.2 g (10.3 mmol) of ethyl pyruvate in 4 ml acetic acid was stirred at 25 bar $H_2$ for 1 h. After filtration, the solvent was removed by distillation (100°C, 20 mbar). The residue was dissolved in ether, $K_2CO_3$ was added, and the mixture was stirred for 1 h. After filtration and removal of the solvent *in vacuo* the crude secondary amine **6** was obtained (95% diastereomeric excess by HPLC). A mixture of the unpurified amine **6** and 200 mg of palladium hydroxide on charcoal in 3 ml ethanol was stirred at 25 bar $H_2$ for 16 h. After filtration, 0.3 ml of $NEt_3$ and 143.5 mg (0.66 mmol) of di-*t*-butyl dicarbonate were added. Removal of the solvent *in vacuo* followed by flash chromatography with hexane/EtOAc (2 : 1) afforded 27.2 mg (31%) of **6b** as a colorless oil. The absolute configuration of **6b** was determined by GC analysis with a chiral column (heptakis-(2,3,6-tri-*O*-methyl)-$\beta$-cyclodextrin in OV 1701-vinyl).

Method B was also used for the preparation of (*S*)-[1-(1-naphthyl)ethyl]isopropylamine **9** (colorless oil, 35% yield).

*Method C (18).* A solution of 280 $\mu$l (1.77 mmol) of amine **4** in 11 ml toluene and 0.65 ml pyridine was cooled to 0°C. Ethyl chloroformate (210 $\mu$l, 2.2 mmol) in 1 ml toluene was added dropwise over 15 min. The reaction mixture was warmed to room temperature and stirred for 4 h. After quenching with 10 ml of 2 *N* KOH, the aqueous layer was extracted three times with toluene. The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography with EtOAc afforded 363.3 mg (84%) of the carbamate as a yellow solid.

The carbamate (297.6 mg, 1.22 mmol) in 3.5 ml THF was added dropwise to a stirred suspension of 294.4 mg (7.76 mmol) of $LiAlH_4$ in 7 ml THF at 0°C. The reaction mixture was warmed and refluxed for 14 h. After cooling to room temperature excess $LiAlH_4$ was quenched with 0.5 ml water, and then NaOH solution (15%, 0.5 ml) and 0.16 ml water were added. The precipitate was filtered and washed with ether. The filtrate was concentrated *in vacuo* and chromatographed with ethanol/$NEt_3$ (100 : 1) to give (*S*)-[1-(1-naphthyl)ethyl]methylamine **8** (203.7 mg, 90%) as a pale yellow oil.

*Method D (19).* To a solution of 186 $\mu$l (1.17 mmol) of amine **4** in 5 ml hexamethylphosphorous triamide, 196.1 mg (2.34 mmol) of sodium bicarbonate and 465.4 mg (1.17 mmol) of 1,4-butanediol ditosylate were added. The reaction mixture was then stirred at 130°C for 30 h. After cooling to room temperature EtOAc (20 ml) was added. The organic phase was washed five times with water, dried over $K_2CO_3$, and concentrated *in vacuo*. After flash chromatography with EtOAc/$NEt_3$ (100 : 1) (*S*)-*N*-[1-(1-naphthyl)ethyl]pyrrolidine **12** (138.1 mg, 52%) was obtained as a yellow oil.

### *Catalytic Hydrogenation*

The commercial modifiers (*R*)-1-(1-naphthyl)ethylamine (**3**, Fluka) and (*S*)-1-(1-naphthyl)ethylamine (**4**, Fluka) were used without further purification. Ethyl pyruvate (Aldrich) was freshly distilled under vacuum before each reaction. A 5 wt% Pt/alumina catalyst (Engelhard 4759) with a metal dispersion of 22% (determined by CO chemisorption (20)) was used in all experiments.

The hydrogenation was carried out in a 100-ml stainless-steel autoclave (Baskerville) with a 50-ml glass liner and PTFE cover. Under standard conditions, 100 mg catalyst, 6.2 $\mu$mol modifier, 10 ml (0.09 mol) EP, and 20 ml acetic acid were used. The reaction mixture was magnetically stirred at 1250 rpm under 10 bar hydrogen at 298 K. Before use the catalyst was prereduced at 673 K for 1.5 h in a hydrogen flow of 30 ml $min^{-1}$ and transferred into the reactor under solvent with the exclusion of oxygen. The catalyst was first contacted with the solvent containing the proper amount of modifier. Reaction temperatures represent the controlled temperature of the bath into which the autoclave was immersed.

The highest initial rate was achieved after the following oxidative pretreatment: 100 mg prereduced catalyst was mixed in 20 ml acetic acid in air for 1 h in an ice bath (by the end of this period the solvent was solid!); 12.4 $\mu$mol modifier **6** was added and the slurry was mixed at 298 K for 2 h in air, then EP was added and the hydrogenation reaction was performed at 10 bar.

The initial reaction rate was calculated from the hydrogen consumption measured by a gas flow controller (Büchi BPC 9901). The enantiomeric excess and conversion were determined by a HP 5890A gas chromatography, using a chiral WCOT Cyclodextrin-$\beta$-2,3,6-M-19 (Chrompack) capillary column. The enantioselectivity is expressed as ee $(\%) = 100 \times (|[R]-[S]|)/([R]+[S])$.

It was found that under standard conditions ee was within a range of $\pm 1\%$, independent of the conversion (between 32 and 100%). This fluctuation is within the range of the standard deviation of the analytical method.

## RESULTS

### *Influence of Reaction Conditions*

A 5 wt% Pt/alumina catalyst modified with (*R*)-1-(1-naphthyl)ethylamine (**3**, Scheme 1) was used in acetic acid in the enantioselective hydrogenation of ethyl pyruvate to (*R*)-ethyl lactate. The influence of catalyst concentration is shown in Fig. 1. The modifier : catalyst weight ratio was kept constant at 0.011, which corresponds to 1.1 molecule of modifier per surface platinum atom ($Pt_s$). There exists a linear relationship between reaction rate and catalyst loading below about 14 g liter$^{-1}$. The deviation from linearity above this value is due to mass transport limitations in the slurry reactor. Accordingly, a catalyst loading of 3.6 g liter$^{-1}$ was used in further experiments which ensured the reactor was working in the kinetic region. The enantioselectivity

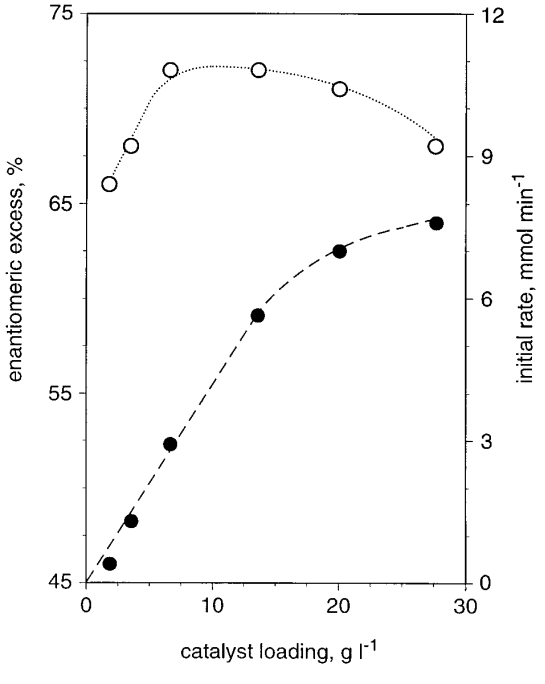



**FIG. 1.** The influence of catalyst concentration on the initial rate (●) and enantiomeric excess (○) under otherwise standard conditions.

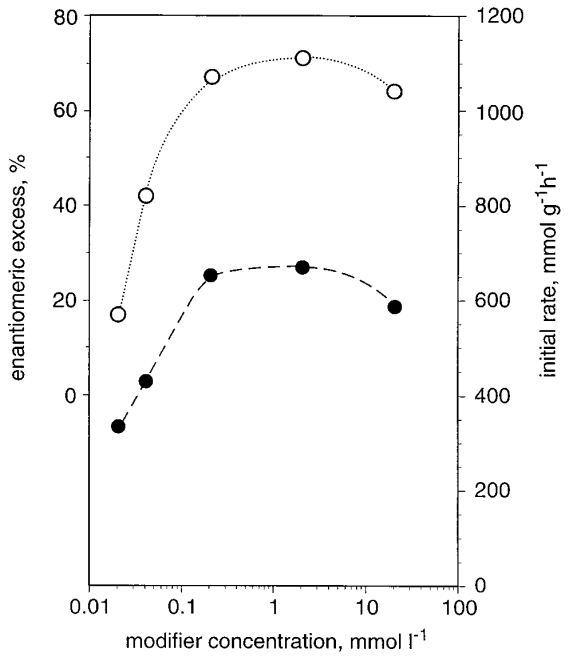



**FIG. 2.** Initial rate (●) and enantiomeric excess (○) as a function of modifier concentration in acetic acid under otherwise standard conditions.

reached its broad maximum above 7 g liter$^{-1}$. There seems to be no clear correlation between ee and the hydrogen supply. Both high hydrogen supply (low catalyst loading) and low hydrogen supply (high catalyst loading) result in lower ee's.

The influence of the modifier concentration on ee and initial rate is illustrated in Fig. 2. Both rate and ee increase with ascending modifier concentration and reach a broad maximum between 0.2 and 20 m*M*. For the lower value, the corresponding modifier : reactant molar ratio is 1 : 15000 and the modifier : $Pt_s$ molar ratio is 1 : 1. For comparison, when cinchona alkaloids are used as modifiers for Pt/alumina in the same reaction, the modifier : $Pt_s$ ratio at the maximum in ee is less than 0.1 in acetic acid and 0.25 in toluene (6, 21).

The remarkably strong effect of temperature is shown in Fig. 3. The initial rate increases with ascending temperature but reaches a plateau at 318 K, whereas selectivity decreases rapidly above 288 K. Similarly, a hydrogen pressure higher than 10 bar has a detrimental effect on ee, without a considerable influence on the reaction rate (Fig. 4). We propose that the negative effect at pressures higher than 10 bar and temperatures higher than 288 K is due to the partial hydrogenation of the naphthalene ring of modifier **3**. A similar phenomenon was observed in the hydrogenation of EP when Pt/alumina was modified with **2** (15). The partial saturation of the unsubstituted naphthalene ring (as identified by NMR analysis (15)) weakens the adsorption of the modifier on Pt and results in a loss in ee. The higher the temperature and/or the hydrogen pressure during reaction, the higher is the extent of this undesired side reaction. Under

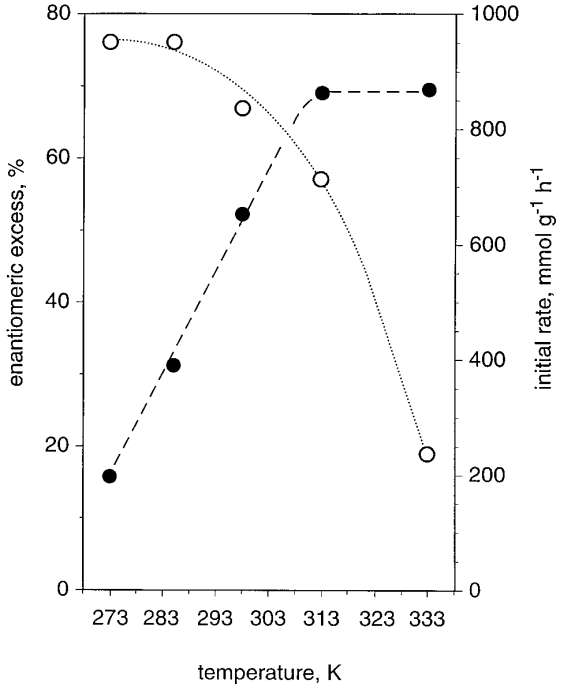



**FIG. 3.** Influence of reaction temperature on the enantiomeric excess (○) and initial rate (●) under otherwise standard conditions.

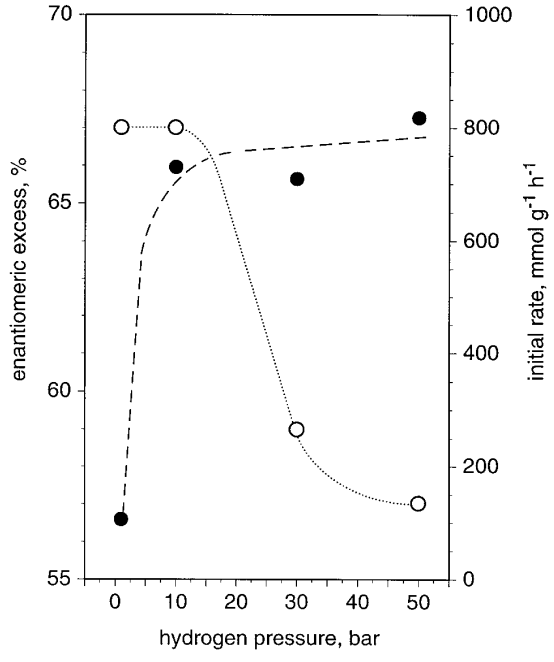



**FIG. 4.** Initial rate (●) and enantiomeric excess (○) as a function of hydrogen pressure under otherwise standard conditions.

mild conditions the stability of the modifier is high enough to provide good ee. Note that Pt is one of the best noble metal catalysts for the hydrogenation of an aromatic ring under relatively mild conditions (22).

The choice of solvent is of crucial importance, as illustrated in Table 2. In contrast to pyruvate hydrogenations over Pt modified with **1** or **2** (15, 23), modifier **3** is only effective in acetic acid. Other polar solvents, such as ethanol or water, and apolar solvents like toluene resulted in low ee and moderate reaction rate.

It is seen in Figs. 1–4 and Table 2 that the initial rate of pyruvate hydrogenation is accelerated in the presence of modifier **3** by a factor of up to 6, compared to the unmodified reaction (120 mmol g$^{-1}$ h$^{-1}$). This effect is comparable to the rate acceleration observed in the presence of cinchona alkaloids or **2** as modifiers (7, 15, 24).

Optimization of a limited number of parameters (pressure, catalyst : modifier and catalyst : reactant ratios) has been attempted at a fixed temperature of 282 K, using factorial design and gradient method. At the optimum, 82% ee was achieved at full conversion. The optimum conditions were : 8 bar, 13 g liter$^{-1}$ catalyst concentration, catalyst : reactant weight ratio = 0.038, $Pt_s$ : modifier **3** molar ratio = 8.1. At the temperature used, the influence of pressure below 10 bar was negligible. For comparison, the same Pt/alumina catalyst afforded 73% ee at 1 bar and 87% ee at 75 bar in the presence of 10,11-dihydrocinchonidine **1b** under similar conditions (13). It is worth mentioning that no data could be found in the literature, according to which 75% or higher ee can be achieved with cinchonidine or its derivatives at pressures of 10 bar or below (25). The best enantioselectivity reported to date for the Pt–**1b** system is 92% ee (95% ee for **1c**) at 100 bar (6).

*Modifier–Reactant Interaction*

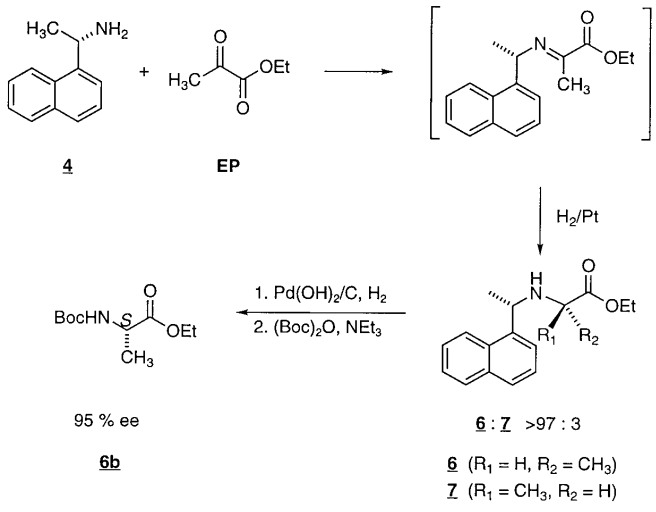
An interesting feature of this enantioselective hydrogenation reaction is that the primary amino group of naphthylethylamine **3** or **4** and the keto group of EP, which is activated by the neighboring ester group, react with each other under reaction conditions (16, 26). The resulting

**TABLE 2**

**Influence of Solvent on Initial Rate ($r_0$) and Enantiomeric Excess (ee) in the Enantioselective Hydrogenation of Ethyl Pyruvate on Pt/Alumina Catalyst Modified with 3 or 6 (Standard Conditions)**

| Solvent | ee (%) | | $r_0$ (mmol g$^{-1}$ h$^{-1}$) | |
|---|---|---|---|---|
| | **3** | **6** | **3** | **6** |
| Acetic acid | 67 | 68 | 730 | 770 |
| Ethanol | 29 | 50 | 125 | 330 |
| Ethanol + acetic acid[a] | 22 | — | 215 | — |
| Toluene | 10 | 9 | 160 | 310 |
| Toluene + acetic acid[a] | 13 | — | 127 | — |
| Water | 10 | — | 260 | — |
| Acetic acid : water = 3 : 1 (*v*/*v*) | 28 | — | 204 | — |

[a] 35 $\mu$mol acetic acid.




SCHEME 2

imine is subsequently reduced on the Pt surface, affording a secondary amine (Scheme 2). This secondary amine is the actual active modifier in the hydrogenation of EP. Further reductive alkylation with ethyl pyruvate to a tertiary amine would require elevated temperature (27) and does not take place under reaction conditions.

NMR analysis of the reaction mixture showed that naphthylethylamine **3** is quantitatively consumed during the hydrogenation reaction and converted to the secondary amine **5** (Table 1) and minor amounts of unidentified products (presumably di- or tetrahydronaphthalene derivatives). When modifier **5** or the corresponding (*S*)-enantiomer **6** was synthesized, purified, and used as a modifier in the hydrogenation of EP, the enantioselectivity was essentially the same in acetic acid and toluene as those observed with **3** and **4** (Table 1). Interestingly, the formation of **5** and **6** from **3** and **4**, respectively, is a highly diastereoselective reaction (95% diastereomeric excess; Scheme 2) (26, 28). The absolute configuration of the newly formed stereogenic center was determined by transformation to the (*S*)-alanine derivative **6b**.

Using a different method for reductive alkylation of **4** with EP allowed the preparation of both diastereoisomers (*S,S*)-**6** and (*S,R*)-**7** (see Experimental section). Unexpectedly, both (*S*, *S*)-**6** and (*S,R*)-**7** induced the same enantioselectivity in the hydrogenation of EP. A control experiment showed that less than 3% isomerization of **7** to **6** occurs during the reaction. This implies that the results obtained with **7** are significant and that the configuration at the stereogenic center in $\alpha$ position to the ester group has no influence on the enantioselection of modifiers **6** and **7**.

Reductive alkylation of **4** with different aldehydes or ketones provides easy access to a variety of related modifers such as **8**–**11**. (Note that the absolute configuration of **11a** and **11b** is not known; only their relative configuration is clear.) The pyrrolidine derivative **12** was prepared by alkylation with 1,4-butanediol ditosylate. None of these modifiers can compete with **6** or **7** (Table 1).

Although reductive amination of **3** with EP is fast under the hydrogenation conditions in acetic acid, this is not necessarily the case in other solvents. We compared the efficiency of modifiers **3** and **6** in different solvents (Table 2). As mentioned above, both compounds provide essentially the same ee's and initial rates in acetic acid at medium pressures. The ee's in toluene are very low with both compounds; however, in ethanol **3** and **6** provide distinctly different ee's (29 vs 50% ee), indicating the reductive amination leading to **6** is slower than hydrogenation of EP in this solvent. The reason for the low ee measured in toluene is not yet clear. Interestingly, the enantioselectivities observed with modifiers **1a**, **1b**, or **2** in acetic acid and toluene were comparable (within a 10% range) (6, 15).

### *Catalyst Pretreatment*

Orito *et al.* (29) reported first that catalyst pretreatment can substantially improve the ee in the hydrogenation of $\alpha$-ketoesters. On the basis of this observation, we also tested the effect of various reductive and oxidative catalyst pretreatment procedures at 273–673 K. Using modifier **6**, none of these procedures provided higher ee than 68% (standard hydrogenation conditions, Table 2). However, oxidative treatment of the prereduced catalyst in acetic acid at 273–298 K, in the presence or absence of modifier, increased the initial rate from 770 to 1060–1550 mmol $g^{-1}h^{-1}$ (see Experimental section for descriptions of the best conditions).

To examine the effect of pretreatment on the catalyst structure, an *in situ* FTIR study of 5 wt% Pt/alumina was carried out. This study, completed with temperature-programmed oxidation experiments, indicated that there is a considerable cleaning of the catalyst surface during prehydrogenation at 673 K. The removal of organic species (presumably residues from the Pt-precursor) is accompanied by CO generation resulting from a decarbonylation reaction catalyzed by Pt at this elevated temperature. An oxidative treatment at 273–298 K (after prehydrogenation at 673 K) completes the purification of the active sites, which is shown by the increase of the initial rate of EP hydrogenation by 50–100%. More details of the FTIR analysis will be published elsewhere.

## DISCUSSION

The kinetic analysis of EP hydrogenation over Pt/alumina, modified with (*R*)-1-(1-naphthyl)ethylamine (**3**, Scheme 1) and the limited optimization of reaction conditions revealed that up to 82% ee can be achieved at 282 K and at hydrogen pressures below 10 bar. At low pressure this new modifier is more efficient than cinchonidine **1a** or 10,11-dihydrocinchonidine **1b**.

Separation and identification of the modifier after EP hydrogenation supplied evidence for the formation of a secondary amine **5** by reductive alkylation of the primary amine **3** with EP. Formation of **5** on the prereduced Pt is assumed to precede the hydrogenation of EP, at least in acetic acid. Modifier **5** and various other derivatives of **3** have been synthesized and tested in EP hydrogenation (Table 1). From the structural analysis we can conclude that the presence of an N–C–C–O structural unit, characteristic of cinchona alkaloids and their derivatives, is not a necessary requirement for enantiodifferentiation in the hydrogenation of $\alpha$-ketoesters. The distance between the O and N atoms can be shorter or even much longer without losing enantioselection. Moreover, the ee can be substantial even in the absence of an oxygen function in the modifier (see, e.g., Table 1). These observations provide strong evidence against a possible modifier–reactant interaction, in which a nucleophilic attraction between the O-atom in the modifier and the ester carbon atom in EP plays a crucial role (30).

The results are in good agreement with our former proposal concerning the nature of enantiodifferentiation in the hydrogenation of EP in acetic acid (12, 31). The interaction of the protonated N-base modifier with the carbonyl O-atom of EP via H-bonding and the sufficiently strong ("fixed") adsorption of the complex on the Pt-surface provide the steric requirements of enantiodifferentiation. Molecular modeling studies of methyl pyruvate hydrogenation over Pt catalysts modified by cinchonidine **1a** or (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol **2** can be found elsewhere (12, 14).

The strong adsorption of the flat aromatic ring ("anchoring" moiety) on a flat Pt surface is a basic requirement in our model (there is substantial evidence for the adsorption of naphthalene parallel to Pt(111) (32–34)). Any deviation from this ideal structure is expected to diminish the enantioselectivity. The partial hydrogenation of the naphthalene ring at pressures higher than 10 bar, resulting in the formation of (5,6,7,8)-tetrahydronaphthalene derivatives (15), distorts the planar structure of the anchoring moiety and lowers the ee. For future improvement of our modifiers, it will be crucial to improve the resistance of the anchoring aromatic ring against hydrogenation. In this way it should be possible to achieve high enantioselectivity also at higher pressure, as with cinchona alkaloids and their most effective derivatives.

## CONCLUSION

(*R*)-1-(1-naphthyl)ethylamine **3** is a versatile and commercially available precursor for the *in situ* preparation of effective modifiers for the platinum-catalyzed enantioselective hydrogenation of ethyl pyruvate. In contrast to the previously used systems, in this case the actual modifier (secondary amine) is formed by reductive alkylation of **3** with the reactant (EP). This reaction offers the opportunity of changing the modifier structure by applying other carbonyl compounds instead of EP. In the low-pressure range (10 bar) the ee reached with this new modifier (82%) is better than those reported with cinchona alkaloids and their derivatives. For use at high pressure the resistance of the anchoring group (naphthalene) against hydrogenation needs to be improved. The studies also indicate that the earlier proposal concerning the importance of the N–C–C–O structural unit (7) does not hold for the (*R*)-1-(1-naphthyl)ethylamine derived modifiers presented in this work.

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