Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Molecular Catalysis A: Chemical 236 (2005) 227–238
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

# Effect of modifier structure in asymmetric 1-phenylpropane-1,2-dione hydrogenation

Igor Busygin [a], Esa Toukoniitty [b], Reko Leino [a,1], Dmitry Yu. Murzin [b,*]

[a] *Department of Organic Chemistry, Åbo Akademi University, FIN 20500, Turku-Åbo, Finland*
[b] *Laboratory of Industrial Chemistry, Process Chemistry Centre, Åbo Akademi University, FIN 20500, Turku-Åbo, Finland*

Received 8 March 2005; accepted 22 April 2005

**Abstract**

Sixteen chiral catalyst modifiers including the natural cinchona alkaloids cinchonidine, cinchonine and quinine together with their several analogues were studied in the hydrogenation of 1-phenylpropane-1,2-dione over a 5% $Pt/Al_2O_3$ catalyst at 10 bar $H_2$ and 15 °C. The influence of the different functional parts of the cinchona alkaloid on the reaction rate, enantio and regioselectivity and diol distribution was investigated. The modifier hydroxyl group in C-9 position is crucial for achieving high enantioselectivity. Replacement of the 9-OH group with a methyl ether results in a complete loss of enantioselectivity for cinchonidine and quinine, whereas an inversion of enantioselectivity was observed for the cinchonine-based modifiers. The role of the absolute configuration at C-8 and -9, the bicyclic quinuclidine part and aromatic system of the cinchona alkaloid on the reaction kinetics was studied as well. Acetic acid is detrimental for enantioselectivity in the hydrogenation of 1-phenylpropane-1,2-dione to the corresponding hydroxyketones whereas in the second hydrogenation step from hydroxyketones to diols, high enantiomeric excesses are observed. The results obtained demonstrate the principal dissimilarity in the enantiodifferentiating mechanism between the well-investigated α-keto esters and vicinal diketones.


*Keywords:* Enantioselective hydrogenation; Chiral modifiers; Cinchonidine; 1-Phenylpropane-1,2-dione; Platinum catalyst

## 1. Introduction

The mechanism of asymmetric induction over chirally modified metal surfaces has been extensively studied. Most of the hitherto-reported investigations have focused on supported Pt and Pd catalysts modified by cinchona alkaloids [1–6]. Despite the recent progress in the field, the nature of the chiral site and the enantiodifferentiating reactant–modifier–metal interactions remain largely unknown and speculative. Suitable experimental techniques and theoretical methods for in situ monitoring and description of asymmetric hydrogenation over a real chirally modified supported metal catalyst under actual operating conditions do not yet exist. Thus, empirical determination of modifier structure–selectivity correlations is still the most frequently pursued approach for investigating the mechanism of heterogeneous enantioselective hydrogenation [7–10]. Studies on the influence of modifier structure on reaction rate and enantioselectivity provide valuable information for understanding and construction of experimentally feasible reaction mechanisms. Hydrogenation of vicinal diketones including butane-2,3-dione [11–13], hexane-3,4-dione [11], cyclohexane-1,2-dione [14], 1,2-diphenyl-1,2-dione [15], hexane-2,3-dione [11], and 1-phenylpropane-1,2-dione (A) [16,17] over chirally modified Pt catalysts represents an extension to the Orito et al. reaction [18] providing in some cases high enantiomeric excesses (ee) of the corresponding chiral alcohols. For asymmetrically substituted vicinal diketones, such as A, the reaction is inherently complex as the presence of two reactive keto groups raises issues of both regio and enantioselectivity. At high conversions, a product mixture consisting of four

* Corresponding author. Tel.: +358 2 215 4985; fax: +358 2 215 4479.
*E-mail addresses:* reko.leino@abo.fi (R. Leino), dmurzin@abo.fi (D.Yu. Murzin).
[1] Fax: 358 2 2154866.

1381-1169/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2005.04.016

different hydroxyketones and four diols may be obtained, as illustrated in Scheme 1. Some of the products obtained in the hydrogenation of A, are important as chiral building blocks for the synthesis of pharmaceutically active substances, e.g. the main product (*R*)-1 (phenylacetylcarbinol, PAC) (Scheme 1) is utilized in the synthesis of ephedrine [19].

Some evident mechanistic analogies exist between the hydrogenations of vicinal diketones and α-keto esters [1–6] over chirally modified catalysts. In both cases, the dependence of rate and enantioselectivity on the catalyst properties (pretreatment, activation, structure) and modifier concentration are similar. However, there are also significant differences, e.g. the lack of overall rate acceleration in the enantioselective hydrogenation, the detrimental role of acetic acid and the influence of C-9 OH group of cinchonidine are characteristic for the diketone hydrogenation while not observed in the hydrogenation of keto esters.

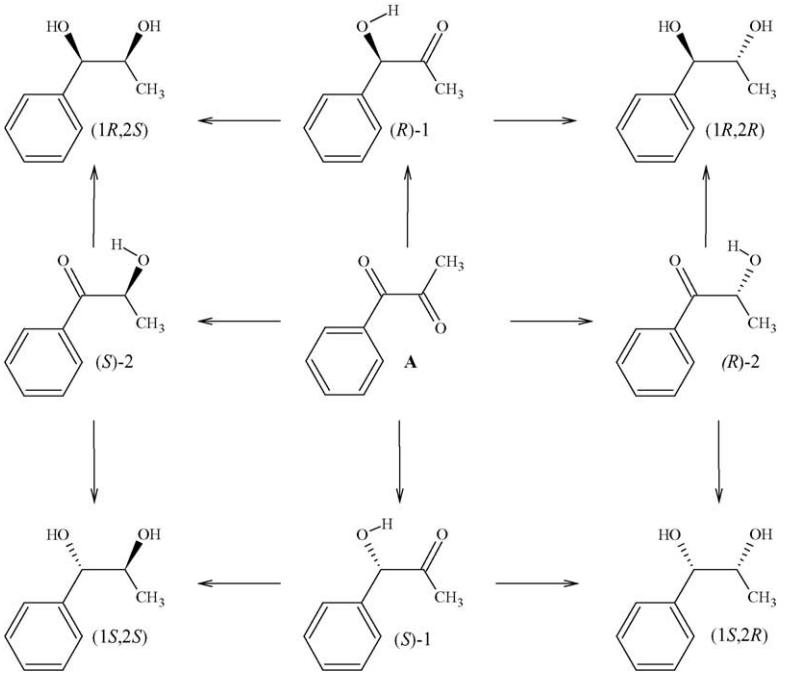
In previous work, we observed slightly improved enantiocontrol in the hydrogenation of A to (*R*)-1 by use of a cinchonidine derivative with sterically demanding substitution in the 11-position of the modifier [20]. In ethyl acetate, the hydrogenation of A over $Pt/Al_2O_3$ modified by 11-(triethoxysilyl)-10,11-dihydrocinchonidine resulted in an increase of ee from 56 to 70% in comparison to cinchonidine, indicating that distal modifier substitution in the C10–11 region may influence both the enantioselectivity and hydrogenation rate. Also, we were able to obtain higher enantioselectivities than observed for the parent modifier Cd. In α-keto ester hydrogenation, the influence of modifier structure has recently been elucidated in detail by Blaser and coworkers by use of several structurally modified cinchona alkaloid derivatives [9,10].

The aim of the present study was to investigate the effect of chiral modifier structure on the enantiodifferentiation in 1-phenylpropane-1,2-dione (A) hydrogenation over chirally modified Pt. Sixteen different chiral modifiers including Cd, Cn, quinine (Qn) and their closely related analogues or derivatives (Scheme 2), many of which were recently evaluated in α-keto ester hydrogenations [9] were employed in order to clarify the modifier structure–selectivity-activity relationships in toluene and/or acetic acid.

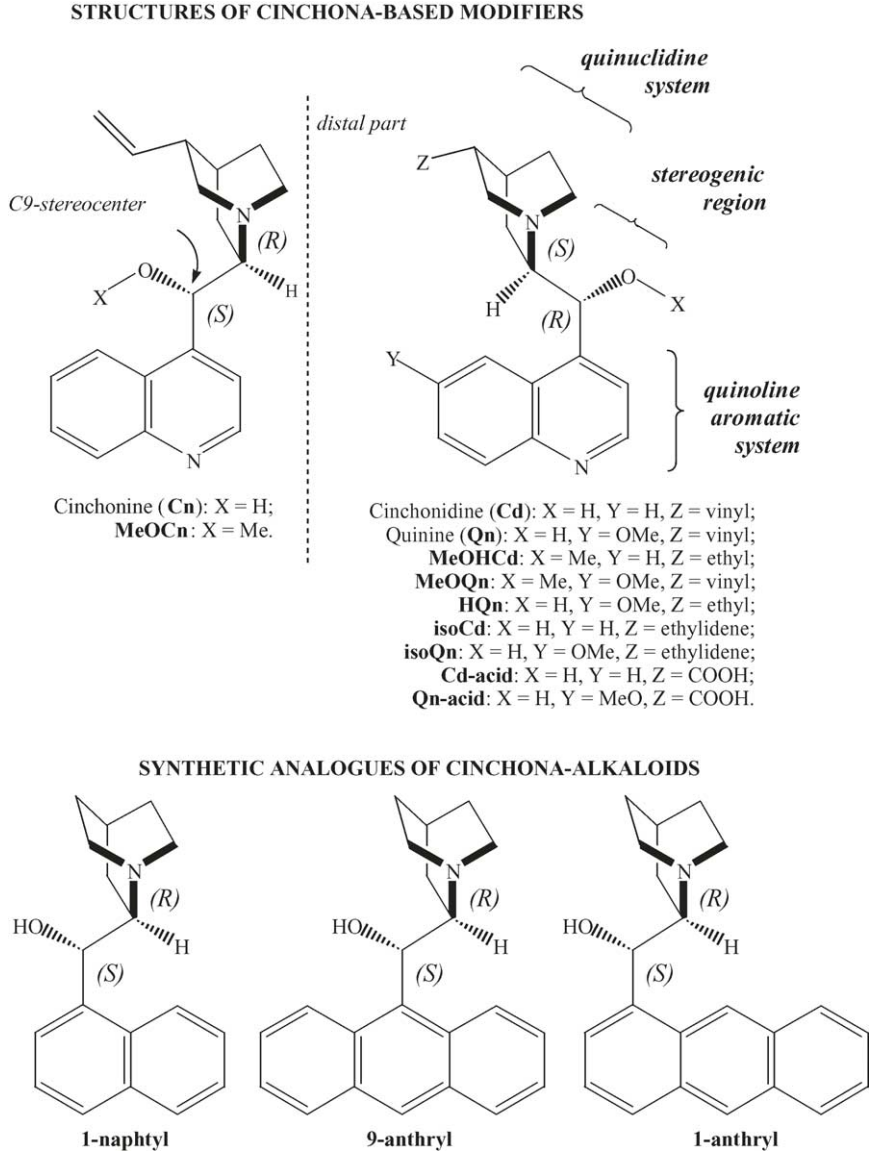
## 2. Experimental

### 2.1. Catalyst and chemicals

A commercial 5 wt.% $Pt/Al_2O_3$ catalyst (Strem Chemicals, 78–1660) was used in the hydrogenations (BET specific surface area 95 $m^2\,g^{-1}$, the mean metal particle size 8.3 nm (XRD), dispersion 40% ($H_2$ chemisorption), the mean catalyst particle size 18.2 μm (Malvern)). Catalyst characterization has been described in detail previously [16]. 1-Phenylpropane-1,2-dione (Aldrich, 22303-4, 99%) was vacuum-distilled before using. Toluene (J.T. Baker, 8077, >99.5%), acetic acid (J.T. Baker, 6052, 99.9%), cinchonidine (Fluka, 27350, 98%), quinine (Aldrich, 14,590-4, 90%, remainder hydroquinine), hydroquinine (Aldrich, 337714-1G, 98%), cinchonidine hydrochloride (C-0894), cinchonine (Fluka, 27370, 85%, remainder 15% dihydrocinchonine) were used as received. The synthesis and characterization of




Scheme 1. Reaction scheme of 1-phenylpropane-1,2-dione (A) hydrogenation.




Scheme 2. Structures and functional parts of modifiers.

the other modifiers used in the present work have been described elsewhere [8,9].

### 2.2. Hydrogenation experiments

1-Phenylpropane-1,2-dione (A) was hydrogenated in a pressurized batch reactor (Parr, 300 $cm^3$). The hydrogen (AGA, 99.999%) pressure and temperature were 10 bar and 15 °C, respectively. The catalyst mass and liquid volume were 100 mg and 100 $cm^3$, respectively, and the stirring velocity was 2000 rpm. The catalyst was activated under hydrogen flow (50 $cm^3$/min) for 2 h at 400 °C and cooled down to the reaction temperature. The pre-activated catalyst could be stored under air minimum 3 days without loss of activity or selectivity. The start up procedure was as follows: the pre-activated catalyst and solvent (50 $cm^3$) containing dissolved modifier ($3.4 \times 10^{-5}$ mol, corresponds to a 10 mg of cinchonidine) were loaded into the reactor and flushed with hydrogen for 20 min at 1 bar. The reactant solution (50 $cm^3$) was saturated with hydrogen for 10 min in a separate injection chamber and injected into the reactor after which the reaction was commenced immediately by starting the agitation. In this way contact of the modifier with the reactant could be eliminated prior to the reaction. Despite careful cleaning of the reactor system, sometimes residues of the modifier remained in the reactor inducing enantioselectivity during racemic hydrogenation. Therefore, a common practice was to carry out a racemic reaction between two modified reactions in order to verify that no modifier contamination remained in the reactor system. The initial concentrations of 1-phenylpropane-1,2-dione and modifier were 0.05 mol $dm^{-3}$ and $3.4 \times 10^{-4}$ mol $dm^{-3}$, respectively.

### 2.3. Definitions of selectivities

Enantiomeric excesses of (*R*)-1-hydroxy-1-phenyl-2-propanones and (*R*)-2-hydroxy-1-phenyl-1-propanones, (*R*)-1 and (*R*)-2, respectively, are defined:

$$ee_{(R)\text{-}1} = \frac{[(R)\text{-}1] - [(S)\text{-}1]}{[(R)\text{-}1] + [(S)\text{-}1]} 100\%$$

$$ee_{(R)\text{-}2} = \frac{[(R)\text{-}2] - [(S)\text{-}2]}{[(R)\text{-}2] + [(S)\text{-}2]} 100\%$$

The diol $S_i$ selectivity has been defined accordingly

$$S_i = \frac{[i]}{[1S, 2S] + [1R, 2R] + [1R, 2S] + [1S, 2R]} 100\%$$

The regioselectivity (rs) is defined

$$rs = \frac{[(R)\text{-}1] + [(S)\text{-}1]}{[(R)\text{-}2] + [(S)\text{-}2]}$$

### 2.4. Analytical procedure

Samples were withdrawn from the reactor at different time intervals and analyzed with a Varian 3300 gas chromatograph (GC) equipped with a chiral column (β-Dex 225). Details of the analytical procedure, calibration and GC standard synthesis can be found in [16].

## 3. Results and discussion

### 3.1. General reaction scheme

The first stage of the hydrogenation of A produces two regioisomers, 1-hydroxy-1-phenylpropanone and 2-hydroxy-1-phenylpropanone, the former one being the major product. Both regioisomers exist as pairs of enantiomers ((*R*)-1 + (*S*)-1 and (*R*)-2 + (*S*)-2, respectively) (Scheme 1). In the presence of chiral modifiers, these intermediate hydroxyketones react further to diols with different rates causing kinetic resolution and increase of the enantiomeric excess at high conversion. The main diols obtained are (1*S*, 2*R*) and (1*R*, 2*S*), respectively. The predominant product distribution can be controlled by changing the solvent and/or the chiral modifier.

### 3.2. Modifier structure

Based on the earlier extensive studies on the hydrogenation of α-keto esters, [7,9,10] three functional parts of the cinchona alkaloid modifiers can be distinguished having mechanistic relevance in the hydrogenation reaction (Scheme 2) namely the stereogenic region, the bicyclic quinuclidine part and the anchoring quinoline ring part.

#### 3.2.1. The stereogenic region

The absolute configuration of the stereogenic region, embrasing C-9 and 8 determines the stereochemistry of the product. The natural cinchona alkaloids contain five asymmetric atoms (C-3, -4, -8, -9 and the quinuclidine-N); however, they differ in configuration only at C-8 and -9. While cinchonidine (Cd) and cinchonine (Cn) bear a diastereomeric relationship, they are often called "near-enantiomers" or "pseudo-enantiomers" as they induce an excess of opposite product chirality in hydrogenations. However, the effect is non linear in toluene and the cinchonine (Cn)-modified $Pt/Al_2O_3$ catalyst yields (*S*)-1 in 27% $ee_{(R)\text{-}1}$, which is 50% less than the 55% $ee_{(R)\text{-}1}$ of (*R*)-1 using Cd [21] (Table 1 and Fig. 1) in toluene. The reaction rate with Cd is two-fold higher than with Cn, although the reaction without any modifier was always faster. Significant differences in regioselectivity were not observed for Cd versus Cn.

Considering the diastereomeric relationship of Cd and Cn, the difference in the magnitude in ee is easily explained by differences in transition state energies in the corresponding enatiodifferentiating steps. Furthermore, the reactions with the two modifiers may proceed by mechanistically different reaction paths or by predominance of one out of different competing paths. It has been observed with other substrates, e.g. 2,2-diethoxyacetophenone that Cn also induces lower ee than Cd, (Table 2) [9,10].

It should be born in mind that the commercially available Cd and Cn, commonly used as such are not analytically pure

Table 1
The initial reaction rate, enantiomeric excess ee over modified catalysts in toluene

| Modifier/solvent | $ee_{(R)\text{-}1}$[a] (%) | $ee_{(R)\text{-}2}$[a] (%) | rs[a] | Initial rate[b] |
|---|---|---|---|---|
| Cd/ethyl acetate | 49 | −24[c] | 3.8 | 12.2 |
| CdHCl/ethyl acetate | 58 | −9[c] | 5.0 | 7.4 |
| Cd/toluene | 55 | 12 | 4.5 | 18.6 |
| Cn/toluene | −27[c] | 14 | 4.4 | 7.5 |
| Qn/toluene | 35 | 12 | 3.8 | 9.1 |
| MeOHCd/toluene | −2[c] | 3 | 2.7 | 16.8 |
| MeOCn/toluene | 16 | −20[c] | 3.0 | 15.8 |
| MeOQn/toluene | −3[c] | −2[c] | 2.7 | 17.7 |
| isoCd/toluene | 44 | 20 | 4.2 | 14.2 |
| Cd-acid/toluene | 0 | 0 | 4.3 | 26.9 |
| isoQn/toluene | 15 | 9 | 2.9 | 8.2 |
| Qn-acid/toluene | 0 | 0 | 4.8 | 33.2 |
| HQn/toluene | 28 | 14 | 3.4 | 6.9 |
| 1-Naphtyl/toluene | 15 | 1 | 2.5 | 13.3 |
| 9-Anthryl/toluene | −9[c] | −11[c] | 2.7 | 7.0 |
| 1-Anthryl/toluene | −9[c] | −3[c] | 3.3 | 6.2 |
| MeNCdI/toluene | 0 | 0 | 2.9 | 26.8 |
| -/Toluene | 0 | 0 | 4.1 | 21.2 |
| Cd/AcOH | 7 | 12 | 4.1 | 13.5 |
| CdHCl/AcOH | 0 | 23 | 5.0 | 7.4 |
| Cn/AcOH | −8[c] | 11 | 5.5 | 14.3 |
| MeOHCd/AcOH | −2[c] | 28 | 4.5 | 18.6 |
| MeOCn/AcOH | −8[c] | 6 | 4.3 | 6.7 |
| MeNCdI/AcOH | 0% Conversion after 2 h | | | |

[a] At 50% conversion of A.
[b] ($10^{-4} \times$ mol $min^{-1}$ $g^{-1}$ cat).
[c] The excess of (*S*)-enantiomer.

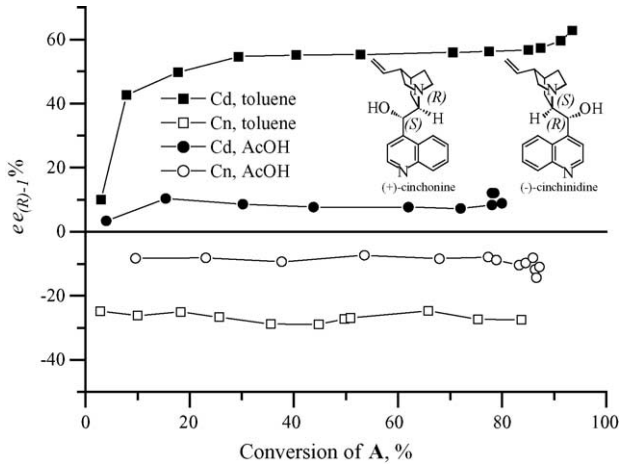



Fig. 1. The $ee_{(R)\text{-}1}$ as a function of reactant conversion: (■) Cd in toluene, (□) Cn in toluene, (●) Cd in acetic acid and (○) Cn in acetic acid.

containing variable amounts of other cinchona alkaloids (see Section 2) possibly influencing the outcome of the hydrogenation reactions. Commercial Cn, used in the present work, initially contains approximately 15% of 10,11-dihydrocinchonine (HCn). However, both Cd and 10,11-dihydrocinchonidine (HCd) give similar ee:s and reaction rates when used as chiral modifiers for hydrogenation of A in ethyl acetate, indicating that the saturation/unsaturation of the 10,11-region is insignificant for enantiocontrol [21], as observed also earlier in α-keto ester hydrogenation [10]. Also it has been shown, that under typical hydrogenation conditions, the 10,11-double bond of Cd is rapidly hydrogenated to give HCd as the acting modifier species [22]. Thus by analogy, it can be assumed that the 15% HCn impurity in Cn is not the origin of the observed non linear behavior but more likely the explanation is the diastereomeric nature of Cd and Cn.

In acetic acid, the $ee_{(R)\text{-}1}$ drops considerably (by 70–90%) with both modifiers Cd and Cn whereas the influence on $ee_{(R)\text{-}2}$ is negligible (Table 1 and Fig. 1). Interestingly, the non linearity of Cd and Cn disappears in acetic acid, both modifiers inducing 8% $ee_{(R)\text{-}1}$ (of opposite chirality) and same reaction rate. The detrimental role of acetic acid is specific to the hydrogenation of A, e.g. in ethyl pyruvate hydrogenation acetic acid has a beneficial effect on ee.

Table 2
Comparison of ee with ethyl pyruvate, 2,2-diethoxyacetophenone and 1-phenyl-1,2-propanedione

| Modifier/solvent | Dione (%) | 2,2-Diethoxy acetophenone [9] | Ethyl pyruvate [9] |
|---|---|---|---|
| Cd/toluene | 55 | 80[a] | 69[a] |
| Qn/toluene | 35 | 34 | 75 |
| isoCd/toluene | 44 | 83 | 72 |
| isoQn/toluene | 15 | 32 | 79 |
| MeOHCd/toluene | −2[b] | 0 | 71 |
| MeOQn/toluene | −3[b] | 0 | 58 |
| Cn/toluene | −27[b] | −47[b,c] | −65[b,c] |
| MeOCn/toluene | 16 | 0 | −31[b] |
| Cd/AcOH | 7 | 48[a] | 88[a] |
| Cn/AcOH | −8[b] | −10[c] | −84[b,c] |
| MeOHCd/AcOH | −2[b] | 0 | 91 |
| MeOCn/AcOH | −8[b] | 0 | −85[b] |

[a] Dihydrocinchonidine.
[b] Excess of (*S*)-enantiomer.
[c] Dihydrocinchonine.

### 3.2.2. Substituents at C-9

As shown earlier, the enantioselectivity in the diketone hydrogenation is also influenced by the substituents at C-9 [20,23]. Systematic studies in the hydrogenation of A using three pairs of 9-OH versus 9-MeO substituted chiral modifiers provide further evidences for the beneficial role of the C-9 OH group. As the 9-hydroxyl group of Cd or Qn is replaced by a methoxy group the $ee_{(R)\text{-}1}$ and $ee_{(R)\text{-}2}$ is practically lost. With Cd the $ee_{(R)\text{-}1}$ decreased from 55 to −2% (MeOHCd) and with Qn from 35 to −3% (MeOQn) in toluene. The same was observed also with a bulkier 9-*O*-(trimethylsilyl)-cinchonidine, which gave only 6% ee using ethyl acetate as solvent [20].

The involvement of C-9 OH group is relatively complex as indicated by the inversion of $ee_{(R)\text{-}1}$ and $ee_{(R)\text{-}2}$ observed with the Cn-based modifier when toluene was used as solvent (Table 1 and Fig. 2). Utilization of MeOCn instead of Cn switched the absolute configuration of the products with $ee_{(R)\text{-}1}$ changing from 27% excess of (*S*)-1 to 16% of (*R*)-1 and $ee_{(R)\text{-}2}$ from 14% (*R*) to 20% (*S*). Similar inversion of ee was not observed in acetic acid, where both Cn and MeOCn give 8% ee of (*S*)-1.

Involvement of C-9 OH group has been reported for the Pd catalyzed C=C double bond hydrogenation [24] and in the hydrogenation of "non-activated" C=O bonds in acetophenones [25]. In the hydrogenation of several α-hydroxyketones, the C-9 OH group was needed for high ee [26] and utilization of MeOCd resulted always in low ee. In ethyl pyruvate hydrogenation, substitution of C-9 OH by C-9–$OCH_3$ has a negligible effect on ee with HCd/MeOCd and Qn/MeOQn (Table 2),

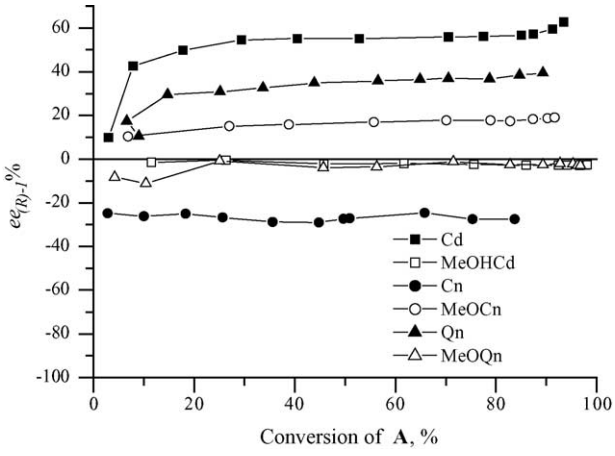



Fig. 2. The enantiomeric excess $ee_{(R)\text{-}1}$ in the hydrogenation of A in presence of chiral modifiers ((●) Cd; (□) MeOHCd; (●) Cn; (○) MeOCn; (▲) Qn; (△) MeOQn) in toluene at 15 °C and 10 bar of $H_2$.

whereas substitution of OH by H or OAc greatly lowers ee [10,27]. With Cn in toluene the ee drops by 50% when MeOCn is used in ethyl pyruvate hydrogenation (Table 2), while the specific 9-MeO-subsitution effect disappears in acetic acid.

A study on the effect of bulkiness of the C-9 substituent in the hydrogenation of ethyl pyruvate, ketopantolactone, 4,4,4-trifluoroacetoacetate and 1,1,1-trifluoro-2,4-diketopentane revealed that relatively small substituents, e.g. MeO- and EtO- do not cause inversion of enantioselectivity and only slightly alter the enantiomeric excess, whereas large bulky substituent in C-9 position notably reduce or invert ee [27]. It was concluded that the MeO-substituent does not notably change the adsorption mode of these modifiers.

### 3.2.3. The bicyclic quinuclidine part

The bicyclic quinuclidine part can be varied by changing the distal substituent in C-3 Z-position (Scheme 2) and also by modification of the quinuclidine-N atom (protonation or alkylation). In reported cases, [22,24,25] alkylation of the quinuclidine-N results in a complete lack of enantioselectivity. This has been interpreted as a direct evidence of the involvement of the quinuclidine-N in the modifier/reactant interaction in the enantiodifferentiating transition state. Recently, a 1-naphtyl-1,2-ethanediol-based modifier without a tertiary nitrogen atom has been reported to be capable of inducing some enantioselectivity in the hydrogenation of ethyl-4,4,4-trifluoroacetoacetate and ketopantolactone indicating that another type of substrate–modifier interactions induces some enantioselectivity as well [28].

### 3.2.4. Role of quinuclidine-N

In order to evaluate the importance of the quinuclidine nitrogen, experiments were conducted with NMeCdI modifier having a methylated quinuclidine nitrogen thus blocking the potential interactions between the substrate and the quinuclidine nitrogen. However, the solubility of NMeCdI in toluene is negligible, and thus the experiments in toluene with NMeCdI gave results identical to a racemic hydrogenation (Fig. 3). The initial reaction rates with NMeCdI and in racemic reaction were the same within experimental error (Fig. 3).

At the same time, with NMeCdI dissolved in acetic acid, no hydrogenation reaction took place in 2 h. This complete inhibition was surprising as in the absence of the modifiers the reaction generally proceeds with similar rates or more rapidly than in the presence of modifier. A possible explanation could be iodine poisoning of the catalyst from the counter ion, which may completely inhibit the hydrogenation reaction. At present, the role of quinuclidine nitrogen cannot be experimentally verified with NMeCdI due to limited solubility in toluene and the possible poisoning effects in acetic acid. However, protonation of the quinuclidine-N does not have negative effects as indicated by high $ee_{(R)\text{-}1}$ of 58% (Table 1) in experiments with cinchonidine hydrochloride modifier (CdHCl) dissolved in ethyl acetate. CdHCl resulted in similar product distribution as Cd in toluene. The protonation of Cd, therefore, is not detrimental for enantiocontrol and the low enantioselectivities in the first hydrogenation step in acetic acid cannot be explained solely by modifier protonation. The possible involvement of acetic acid has been rationalized earlier by the involvement of a three-step reaction mechanism where the formation of modifier–acetic acid–reactant complex is the actor species and in this case responsible for the decreased ee [23].

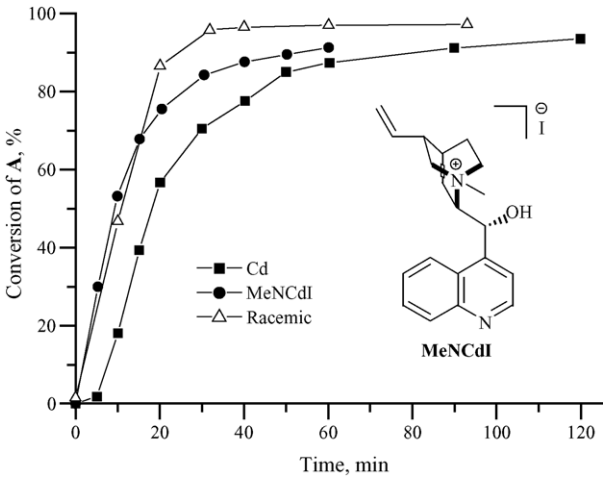



Fig. 3. Hydrogenation kinetics of 1-phenylpropane-1,2-dione in toluene at 15 °C. Catalyst: 5 wt.% $Pt/Al_2O_3$ modified in situ with (■) cinchonidine (Cd); (●) MeNCdI; (△) unmodified platinum.

### 3.2.5. C-3 quinuclidine position (Z)

Tuning of enantioselectivity can be achieved by varying the "substituent at C-3 quinuclidine position" (Z) as demonstrated by the large variance of $ee_{(R)\text{-}1}$ (0–70%) using different Z-substituents. The substituents can in principle influence the conformation of the modifier and electronic properties as well as induce steric effects. The influence of the double bond in 10,11-position on the enantioselectivity cannot be established unambiguously, since it is rapidly hydrogenated under reaction conditions. In experiments with Cd and HCd, the double bond in 10,11-position had a negligible influence [21] whereas with Qn and HQn, the latter resulted in lower $ee_{(R)\text{-}1}$ (Table 1).

Changing position of the double bond from 10,11 (Cd) to 3,10 (isoCd) results in a small negative effect on enantioselectivity (Table 1). Enantiomeric excess dropped down to 44% and 15% with isoCd and isoQn, respectively (Fig. 4). Double bond in these compounds is sterically hindered for adsorption on platinum surface and was not hydrogenated during the reaction (confirmed by GCMS).

Carboxylic acid-substituent in Z position resulted in a lack of enantioselectivity. These modifiers were not completely dissolved in toluene. However, Qn- and Cd-acid were somewhat effective in ethyl pyruvate hydrogenation and induced 48 and 46% ee, respectively, [8] in toluene. Therefore, the complete lack of enantioselectivity was not solely due to lim-

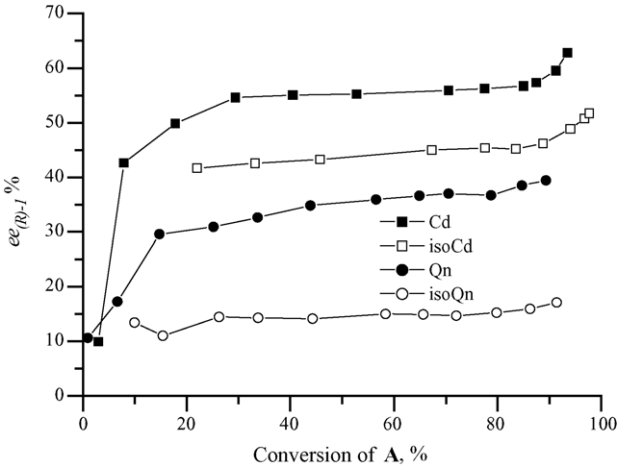



Fig. 4. Hydrogenation kinetics of 1-phenylpropane-1,2-dione in toluene at 15 °C. Catalyst: 5 wt.% $Pt/Al_2O_3$ modified in situ with (■) cinchonidine (Cd); (□) isoCd; (●) quinine (Qn); (○) MeOQn.

ited solubility of these modifiers but rather due to the acid functionality.

Cn with its 1-naphtyl analogue, which does not possess substituent at C-3 position, were compared. The inversion of enantioselectivity was obtained when 1-naphtyl modifier without vinyl group at C-3 position was used indicating that the absolute configuration at C-9 and C-8 does not necessarily determine the main product enantiomer, as was also the case with Cn and MeOCn. Although, Cn and 1-naphtyl have two differences in the structure, the changing of aromatic nitrogen to carbon had a negligible influence both on rate and ee in ethyl pyruvate hydrogenation [8]. It is, therefore, likely that the differences of Cn and 1-naphtyl originate from differences in the C-3 substituents rather than due to differences in the anchoring group.

In the present work modifications to the Z group reduced or inverted the enantioselectivity. Previously, however, a notable positive effect on enantioselectivity of A hydrogenation [20] had been observed when the vinyl group was modified with triethoxy silyl group. The $ee_{(R)-1}$ could be increased from 56 to 70%. Similar observations that the Z-substituent can have either notable positive or negative influence on ee have been reported [8,9] in $\alpha$-keto ester hydrogenation.

### 3.2.6. The quinoline ring

The anchoring quinoline ring can be varied by substitution of one or more aromatic hydrogen atoms or by replacement of the quinoline ring with other aromatic or non-aromatic systems. Extended aromatic ring systems have been most efficient due to strong adsorption on the catalyst metal surface [10]. Hydrogenation of the anchoring aromatic part results in decreased enantioselectivity due to reduced adsorption strength on Pt [10]. Substitution of hydrogen at position 6 in quinoline ring by methoxy group resulted to descent of $ee_{(R)-1}$ from 55% (Cd) to 35% (Qn) (Table 1). Methoxy group can hinder adsorption of modifier by flat aromatic system on catalyst surface. The reaction rate was two-fold higher with Cd. It

Table 3
The product distribution of diols over modified catalysts

| Modifier/solvent | $S_{RR+SS}$ (%) | $S_{RS}$ (%) | $S_{SR}$ (%) | $ee_{RS}$ (%) |
|---|---|---|---|---|
| Cd/ethyl acetate | 17 | 57 | 26 | 36 |
| CdHCl/ethyl acetate | 12 | 66 | 22 | 49 |
| Cd/toluene | 19 | 56 | 25 | 38 |
| Cn/toluene | 14 | 34 | 52 | −21[a] |
| Qn/toluene | 25 | 44 | 31 | 17 |
| MeOHCd/toluene | 18 | 41 | 41 | 0 |
| MeOCn/toluene | 19 | 51 | 30 | 26 |
| MeOQn/toluene | 18 | 40 | 42 | −2[a] |
| isoCd/toluene | 18 | 51 | 31 | 24 |
| Cd-acid/toluene | 17 | 41 | 41 | 0 |
| isoQn/toluene | 21 | 43 | 36 | 8 |
| Qn-acid/toluene | 19 | 40 | 41 | 1 |
| HQn/toluene | 26 | 40 | 34 | 8 |
| 1-Naphtyl/toluene | 16 | 52 | 32 | 23 |
| 9-Anthryl/toluene | 26 | 30 | 44 | −19[a] |
| 1-Anthryl/toluene | 24 | 43 | 33 | −13[a] |
| MeNCdI/toluene | 17 | 42 | 41 | 1 |
| -/Toluene | 17 | 41 | 42 | −1[a] |
| Cd/AcOH | 0 | 16 | 84 | −67[a] |
| CdHCl/AcOH | 0 | 0 | 0 | – |
| Cn/AcOH | 0 | 70 | 30 | 40 |
| MeOHCd/AcOH | 0 | 11 | 89 | −78[a] |
| MeOCn/AcOH | 0 | 83 | 17 | 66 |

[a] The excess enantiomer was (1*S*, 2*R*).

is interesting also to compare MeOHCd and MeOQn and note that those modifiers behave analogously yielding the same rate and regioselectivity in addition to a nearly complete lack of enantioselectivity ($ee_{(R)-1}$, $ee_{(R)-2}$, $ee_{RS}$ Tables 1 and 3).

The effect of quinoline replacement by naphthalene and anthracene was estimated. 1-Naphthyl, 1-anthryl and 9-anthryl modifiers having the same absolute configuration in C-8 and -9 as Cn were tested (Fig. 5). Interestingly, the replacement of anthryl with naphtyl-substituent inverts the ee from excess of (*S*)-enantiomer to excess of (*R*)-enantiomer. The same modifiers in ethyl pyruvate hydrogenation at 10 bar pressure in toluene resulted all in an excess of (*S*)-ethyl lac-

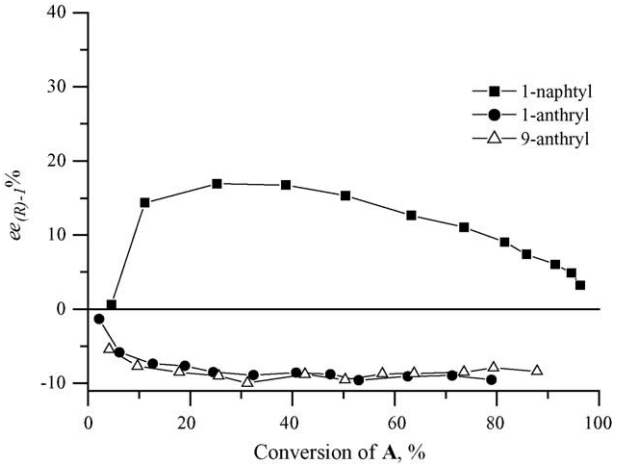



Fig. 5. The enantiomeric excess $ee_{(R)-1}$ in the hydrogenation of A in presence of chiral modifiers ((■) 1-naphtyl; (●) 1-anthryl; (△) 1-anthryl) in toluene at 15 °C and 10 bar of $H_2$.

tate (1-naphthyl ee = 59%, 1-anthryl ee = 10% and 9-anthryl ee = 60%) [8] as can be expected form the same absolute configuration at C-8 and -9 compared to Cn. In comparison, the ethyl pyruvate where the 1-anthryl behaves exceptionally in hydrogenation of A, the 1-naphthyl has totally different behavior (Fig. 5). To the best of our knowledge similar inversion of ee due to extending the anchoring aromatic part have not been reported previously indicating that in hydrogenation of A is rather specific in terms of structure–selectivity effects.

### 3.3. Reaction rate

It has often been reported that an "overall rate acceleration" is a general feature of the Pt/cinchona system (the Orito reaction) for $\alpha$-functionalized ketones [1–6] and is closely linked with enantioselectivity. For ethyl pyruvate, up to 100-fold increase of reaction rate has been reported [29]. In this light, a noteworthy observation is that the modifiers induce ee and rate deceleration in hydrogenation of A, which is structurally also a $\alpha$-functionalized ketone. The observed rate deceleration was not proportional to enantioselectivity as evidenced by experiments carried out using several different modifiers in toluene and acetic acid. The rate varied a lot having a five-fold difference between the lowest and the highest initial reaction rate (Table 1) and no correlation with enantioselectivity could be found. In cyclohexane-1,2-dione hydrogenation Cd resulted in considerably reduced reaction rate. For butane-2,3-dione, a rate acceleration has been reported over a 5%$Pt/Al_2O_3$ (JM94) catalyst modified with Cd but it is not related necessarily to ee as the same ee can be obtained also without a rate acceleration over a Cd modified 6.3% $Pt/SiO_2$ catalyst. Furthermore, in hydrogenation of butane-2,3-dione using codeine as the catalyst modifier in dichloromethane or ethanol up to five-fold rate acceleration could be observed with zero enantioselectivity [15]. All these experimental observations suggest that in vicinal diketone hydrogenation the "overall rate acceleration" although observable in some cases is not related to enantioselectivity.

### 3.4. Influence of solvent

Solvent plays an important role and ee depends strongly on the solvent polarity [30] in the hydrogenation of A with Cd as the catalyst modifier. Among the tested solvents toluene ($ee_{(R)\text{-}1}$ = 65%) and ethyl acetate ($ee_{(R)\text{-}1}$ = 62%) give the highest $ee_{(R)\text{-}1}$ at maximum yield. Alcohols, e.g. ethanol ($ee_{(R)\text{-}1}$ = 12%) and methanol ($ee_{(R)\text{-}1}$ = 4%) resulted in low $ee_{(R)\text{-}1}$. The detrimental effect of acetic acid for $ee_{1\text{-}OH}$ was obvious (Fig. 1, Table 1) with Cd, Cn and CdHCl. Typically $ee_{(R)\text{-}1}$ is between 50 to 65% in toluene with Cd and is reduced in acetic acid from 10 to 2% depending on the experimental conditions. In acetic acid, utilization of MEOHCd instead of Cd results in a small changes of $ee_{(R)\text{-}1}$ from 7% of (*R*)-enantiomer to 2% of (*S*)-enantiomer (Fig. 6). Replacement of Cn with MeOCn does not affect enantioselectivity. It can

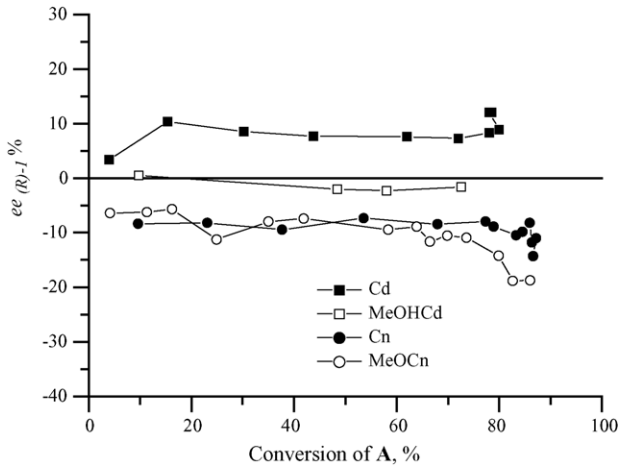



Fig. 6. The enantiomeric excess $ee_{(R)\text{-}1}$ in the hydrogenation of A in presence of chiral modifiers ((■) Cd; (□) MeOHCd; (●) Cn; (○) MeOCn) in acetic acid at 15 °C and 10 bar of $H_2$.

be summarized that in the first hydrogenation step regardless of the modifier structure acetic acid has a negative effect on $ee_{(R)\text{-}1}$.

In ethyl pyruvate hydrogenation acetic acid increases ee compared to toluene (Table 2) and this has been explained by modifier protonation and shifting of conformational equilibrium solely toward the active open(3) conformation (100% in acetic acid versus 70% in toluene, see below). At the same time, analogously to hydrogenation of A also in ketopantolactone [31], some achiral hydroxyl ketones [26], some acetophenones, e.g. 2,2-diethoxyacetophenone (Table 2, [9]), 3,5-bis(trifluoromethyl)-acetophenone [25] and other vicinal diketones exhibit notably reduced ee in acetic acid compared to toluene. Based on high ee obtained in experiments with CdHCl, which is obtained by protonation of the quinuclidine-N, one can exclude that modifier protonation could cause the decreased ee.

### 3.5. Regioselectivity

Regioselectivity was lower (rs = 2.0–3.8, Table 1) in this work compared to previous reports for the same reaction in ethyl acetate [17] (rs = 10, in the absence of modifier rs = 4). However, the C1=O1 group adjacent to phenyl ring reacts mainly in the first step of the reaction yielding 65–80% (*R*)-1 + (*S*)-1. With Cd the rs and ee were interrelated, i.e. high ee and simultaneously high rs were achieved or vice versa. However, in the present work similar correlation cannot be observed (Table 1). This indicates that also rs is affected by structural changes in the modifier.

### 3.6. Product distribution in diols

The final hydrogenation products composed of four diols (Scheme 1), i.e. (1*R*, 2*S*), (1*S*, 2*R*), (1*R*, 2*R*) and (1*S*, 2*S*). The product distribution varied depending on the modifier and solvent. Since (1*R*, 2*R*) and (1*S*, 2*S*) diols could not be

separated completely and therefore in Table 3 their sum is reported.

In toluene during racemic hydrogenation 20% of (1*R*, 2*R*) + (1*S*, 2*S*) and 40% (1*R*, 2*S*) and 40%(1*S*, 2*R*) were formed. Also with modifiers (MeOQn, isoQn, Qn-acid, MeO-HCd, Cd-acid) which produced low $ee_{(R)\text{-}1}$ the diol distribution resembled the racemic product distribution in the absence of modifier. The further reactions of intermediate hydroxyketones are diastereoselective even during the racemic reaction. It can be explained by steric effects, e.g. as (*S*)-1 reacts further to (1*S*, 2*R*) and (1*S*, 2*S*) the adsorption mode favoring the reaction to the former is sterically less constrained as in s-*cis* conformation both hydroxyl and phenyl groups point upwards from the surface (Fig. 7) enabling easier adsorption on metal surface. Applying this steric criteria it can be seen that (*R*)-1 and (*S*)-2 react preferably to (1*R*, 2*S*) and (*S*)-1 and (*R*)-2 react preferably to (1*S*, 2*R*) which are the main diols during a racemic hydrogenation.

In the presence of modifier in toluene, the selectivity towards (1*R*, 2*R*) + (1*S*, 2*S*) varied only slightly (17–26%) indicating that the modifier does not promote selectivity towards (1*R*, 2*R*) + (1*S*, 2*S*). In toluene a general trend, regardless on the structure of the modifier, is that always when an excess of (*R*)-1 is obtained in the first reaction step also an excess of (1*R*, 2*S*) is produced and an excess of (*S*)-1 results in an excess of (1*S*, 2*R*) (Tables 1 and 3). This is a consequence of high diastereoselectivity in the second hydrogenation step, e.g. with CdHCl in the first hydrogenation step and 58% excess of (*R*)-1 compared to (*S*)-1 is produced (corresponding to molar ratio of (*R*)-1 to (S)-1 of about 4-to-1). In the second hydrogenation step, (*R*)-1 reacts to (1*R*, 2*S*) and (*S*)-1 gives preferably (1*S*, 2*R*) due to above-mentioned high diastereoselectivity. Due to the four-fold excess of (*R*)-1 the (1*R*, 2*S*) has been produced in notable excess to (1*S*, 2*R*) resulting in 49% $ee_{RS}$ (Table 3). Therefore, in toluene the modifier does not seem to have notable interactions in the second hydrogenation step and it does not influence the sterochemical outcome of the second hydrogenation step. This was confirmed also by a transient experiment carried out by injecting Cd at about 98% conversion of A and following the reactions of formed racemic hydroxyketones (second hydrogenation step) to diols. During the transient experiment the $ee_{RS}$ remains around zero indicating that the added Cd did not influence the second hydrogenation step, i.e hydrogenation of the racemic hydroxyketone mixture to diols.

In acetic acid, the diol distribution was very different from that of toluene. Practically no (1*R*, 2*R*) and (1*S*, 2*S*) diols were formed under reaction times used in the present work. In MeOHCd and Cd in acetic acid, the main product was (1*S*, 2*R*) having $ee_{SR}$ 78 and 67%, respectively. With MeOCn and Cn the main diol was the (1*R*, 2*S*) with 66 and 40% $ee_{RS}$. It was noted above that in acetic acid the C-9 hydoxyl group does not have similar beneficial effects like in the first hydrogenation step in toluene. As Cd/MeOHCd and MeOCn/Cn were tested in acetic acid the product distribution was similar, and with MeO-derivatives the $ee_{SR}$ and $ee_{RS}$ were higher than with HO-derivatives (Cd and Cn). Therefore, the presence of acetic acid and MeO-substituent is very beneficial in the second hydrogenation step increasing $ee_{SR}$ or $ee_{RS}$. It is interesting mechanistically that the role of acetic acid is not just to protonate the modifier as experiments with protonated CdHCl demonstrate analogous behavior with Cd in toluene. Previously von Arx et al. [32] have proposed a three-step reaction pathway based on experiments with ethyl-4,4,4-trifluoroacetoacetate, where the enantiodifferentiating complex would consist of a modifier, a reactant and a carboxylic acid molecule. Similar mechanism in the second hydrogenation step would include the specific role of acetic acid, however, at present it is not clear how the acetic acid molecule is included in the reactant–modifier complex. The reaction kinetics of hydro-

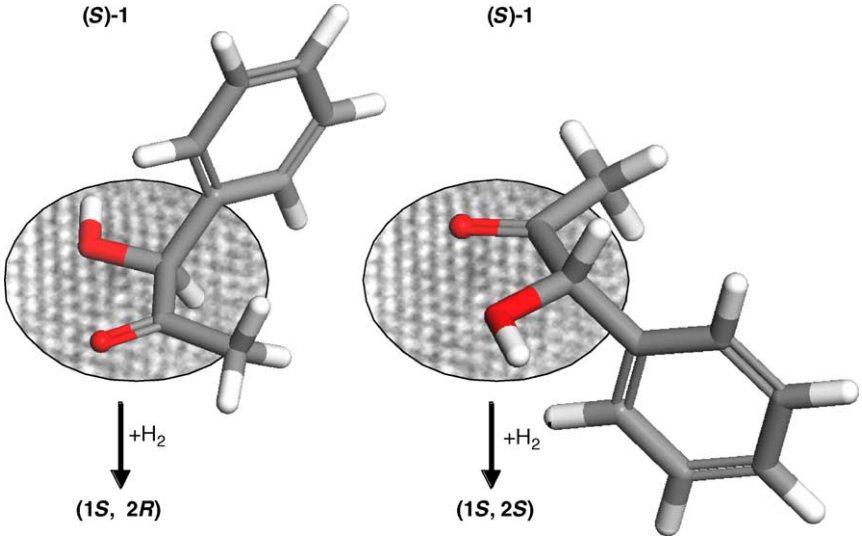



Fig. 7. Schematic representation of the adsorption of (*S*)-1 on a flat surface (Pt particle). The left hand side adsorption mode, leading upon hydrogenation to (1*S*, 2*R*), is much less demanding due to smaller repulsion induced by the C1 HO─ and Ph groups pointing upwards from the surface.

genation of A with MeOHCd in acetic acid demonstrates that in the second hydrogenation step by far the fastest reaction is the further hydrogenation of (*S*)-1 to (1*S*, 2*R*) (Scheme 1), i.e. via reaction of C2=O2 and not the C1=O1 group adjacent to phenyl ring. This can be the explanation why Sonderegger et al. [26] found a very different behavior for some achiral $\alpha$-hydroketones, e.g. 2-hydroxyacetophenone, resembling the reactions of A rather than the second hydrogenation step in the present work.

Due to relatively slow reaction in the second hydrogenation step, the conversion to diols remained low (>30%) in the present work. Therefore, in order to address the selectivities in second hydrogenation step over the whole conversion range much longer reaction times should be used and preferably using intermediate hydroxyketones as starting reactants. However, this is a topic of further studies which aim to find an explanation for the specific involvement of acetic acid in the second hydrogenation step.

### 3.7. Modifier conformation

Cinchona alkaloids can exist in several open and closed conformations in the liquid phase [33]. In the open conformation, the quinuclidine-N atom points away from the quinoline ring and in the closed conformations towards the quinoline ring. Previously for cinchonidine, the open(3) conformation has been proposed to be the actor species in $\alpha$-keto ester hydrogenation [33]. Theory and several experimental observations support this statement. The open(3) conformation is the most abundant in non polar media (toluene) or acetic acid, which are the best solvents for ethyl pyruvate hydrogenation. Furthermore, rigid cinchona alkaloids which exist only in open conformation provide comparable ee with those ones capable of adopting several conformations [34].

Cd exist solely in open(3) conformation in acetic acid with the quinuclidine-N protonated [35] whereas in toluene 70% of open and 30% closed conformers can be found. The changes in the cinchonidine structure can influence the conformational equilibrium. Very little is known about the conformational equilibrium of other cinchona alkaloids used in the present work. Dijkstra et al. [36] have reported that Qn, HQn, Cd and Cn, exist in open(3) conformation in deuterobenzene. For 9-MeO-derivatives no conformational study exists. Therefore, it is difficult to address the role of conformational equilibrium in the present work. Indirect indication of similar conformational behavior of 9-MeO-derivatives and 9-OH-derivatives can be deduced from analogous performance of these modifiers in ethyl pyruvate hydrogenation where the open(3) is assumed to be the actor conformation. Based on above arguments it can be expected that the conformational behavior of Qn, HQn, Cd and Cn as well as MeOHCd, MeOCn, and MeOQn is similar in toluene. Some differences can emerge in acetic acid due to hydrogen bonding to C-9 OH group. However, more important than the conformation in liquid phase is the adsorption mode and conformation of the modifier on the catalyst surface.

### 3.8. Modifier adsorption mode

The adsorption mode of the modifier on the Pt surface gives direct information about the chiral active site as the enantiodifferentiating interactions and hydrogenation steps take place on the Pt surface. Cd has been proposed to adsorb in three different coverage dependent adsorption modes (parallel and two tilted) as evidenced by in situ ATR-IR spectroscopic measurements [37]. Several other spectroscopic measurements support these conclusions concerning Cd adsorption via quinoline moiety [38–41]. The strongly adsorbed parallel mode has been proposed to be the actor species and the tilted modes are considered as spectators. The effect of modifier adsorption mode has been studied by altering the C-9-substituent bulkiness from OH–, MeO–, EtO–, up to very bulky O-aryl and O-silyl-substituents [27]. Relevant to present study was the conclusion that small MeO– group does not change the adsorption mode compared to –OH group. Therefore, the Cd/MeOHCd, Qn/MeOQn and Cn/MeOCn modifier pairs can be assumed to adsorb in a similar mode and the observed effects are due to methylation of the C-9 hydroxyl group rather than changed adsorption mode.

### 3.9. Mechanistic implications and comparison with other substrates

Exner et al. [9] tested many of the modifiers used in the present work with various substrates. From Table 2 a comparison with A, ethyl pyruvate and 2,2-diethoxyacetophenone can be seen. Ethyl pyruvate is rather insensitive to the changes in the modifier structure whereas 2,2-diethoxyacetophenone behaves in a similar way as A. It was noted [9] that reactions of aliphatic ketones (e.g. ethyl pyruvate) differ form reactions of aromatic ketones, the latter ones being more enantioselective in toluene and exhibiting large differences in ee with varying modifier structure whereas the former ones are less sensitive to changes in the modifier structure and give the best ee in acetic acid. This became evident also in the present work. The reactions of C1=O1 (aromatic ketone) resulted in the highest ee in toluene as a solvent and with modifiers having C-9 hydroxyl group. Furthermore, the second hydrogenation step, where the reaction pathway is dominated by reactions of aliphatic $C_2$=$O_2$ group, proceed with high enantioselectivity in acetic acid and with modifiers without C-9 hydroxyl group like MeOHCd.

Many substituted acetophenones, achiral hydroxyketones and $\alpha$-diketones have interesting similarities, e.g. acetic acid has a negative effect compared to toluene and Cd is much more effective than MeOCd indicating that these reactions are mechanistically analogous. All mechanistic models of the cinchonidine–Pt system postulate that the tertiary quinuclidine-N is directly involved in the interaction with the reactant [1–6]. Several models for the cinchonidine–vicinal diketone interactions have been proposed [11,14,23,42], although the actual predominating pathways during the hydrogenation reaction remain speculative. For vicinal diketones,

the proposed complexes contain hydrogen bonding of the reactant into the quinuclidine-N of Cd in open conformation. The reactant has been assumed to adopt either s-*cis* or s-*trans* conformation and a single or bifurcated hydrogen bond [11,14,23,42]. However, as also demonstrated in the present work, the enantiodifferentiation shows a rather complex behavior and dependence on modifier structure and solvent used making these mechanistic proposals rather rough simplifications of the reality. In practice, several competing mechanistic pathways may be present in a single reaction system and the rate and ee thus result from a complex combination of various effects.

## 4. Conclusions

The hydrogenation of 1-phenylpropane-1,2-dione (A) with 16 different modifiers in toluene and acetic acid was studied and the results can be summarized as follows:

- No rate acceleration was observed, the rate with all tested modifiers being equal or lower than the racemic reaction rate.
- Relatively high $ee_{(R)\text{-}1}$ can be obtained (<70%) with the modifiers having C-9 hydroxyl group and using toluene as a solvent.
- $ee_{(R)\text{-}2}$ is relatively low (<28%) and does not depend in a similar way on the solvent and modifier structure as $ee_{1\text{-}OH}$.
- C-9 MeO-substituent and acetic acid are beneficial in the second hydrogenation step, which proceed mainly via hydrogenation of C2=O2 group (aliphatic).
- Protonation of quinuclidine-N is beneficial and cannot explain the detrimental role of acetic acid for $ee_{(R)\text{-}1}$
- Cn-based modifiers (having the same absolute configuration in C8 and C9) exhibited a very strong dependence on the modifier structure and give lower ee than Cd-based modifiers. The inversion of ee was observed upon changing C-9 hydroxyl group (Cn) to a methoxy group (MeOCn) as well as by replacing anchoring aromatic anthracene with a naphthalene group.

The experimentally observed structure–selectivity effects indicate that several competing mechanistic pathways are present in a single reaction system and the rate and enantiomeric excess thus result from a complex combination of various effects. The hydrogenation of A is very complex and mechanistically different from ethyl pyruvate hydrogenation. The present day mechanistic models are by far too simple in order to account for all the observed structure–selectivity-activity effects in the hydrogenation of A. However, the experimentally observed analogies with various substrates (e.g. substituted acetophenones, ketopantolactone, vicinal diketones and $\alpha$-hydroxy ketones) point out to the mechanistic similarities and suggest that these reactions could be rationalized within the framework of a common mechanistic model.

## Acknowledgments

Dr. M. Studer and Dr. C. Exner are gratefully acknowledged for providing a number of modifiers. Financial support from the Academy of Finland (Project No. 201207: “New modifiers for the production of enantiopure compounds”) and the generous support from the Magnus Ehrnrooth foundation is gratefully acknowledged. This work is part of the activities at the Åbo Akademi Process Chemistry Centre within the Finnish Centre of Excellence Programme (2000–2005) by the Academy of Finland.

## References

[1] T. Bürgi, A. Baiker, Acc. Chem. Res. 37 (2004) 909.
[2] M. Von Arx, T. Mallat, A. Baiker, Top. Catal. 19 (2002) 75.
[3] M. Studer, H.-U. Blaser, C. Exner, Adv. Synth. Catal. 345 (2003) 45.
[4] D.Yu. Murzin, P. Mäki-Arvela, E. Toukoniitty, T. Salmi, Catal. Rev.: Sci. Eng. 47 (2005) 1.
[5] P.B. Wells, A.G. Wilkinson, Top. Catal. 5 (1998) 39.
[6] J.L. Margitfalvi, E. Tálas, E. Tfist, C.V. Kumar, A. Gergely, Appl. Catal. A: Gen. 191 (2000) 177.
[7] A. Pfaltz, T. Heinz, Top. Catal. 4 (1998) 229.
[8] C. Exner, Ph.D. Thesis, University of Basel, 2002.
[9] C. Exner, A. Pfaltz, M. Studer, H.-U. Blaser, Adv. Synth. Catal. 345 (2003) 1253.
[10] H.U. Blaser, H.P. Jalett, W. Lottenbach, M. Studer, J. Am. Chem. Soc. 122 (2000) 12675.
[11] J. Slipszenko, S. Griffiths, P. Johnston, K. Simons, W. Vermeer, P. Wells, J. Catal. 179 (1998) 267.
[12] M. Studer, V. Okafor, H.-U. Blaser, Chem. Commun. (1998) 1053.
[13] X. Li, N. Dummer, R. Jenkins, R.P.K. Wells, P.B. Wells, D.J. Willock, S.H. Taylor, P. Johnston, G.J. Hutchings, Catal. Lett. 96 (2004) 147.
[14] O.J. Sonderegger, T. Bürgi, A. Baiker, J. Catal. 215 (2003) 116.
[15] K.E. Simons, Ph.D. Thesis, Hull University, 1994, p. 81.
[16] E. Toukoniitty, P. Mäki-Arvela, M. Kuzma, A. Villela, A. Kalantar Neyestanaki, T. Salmi, R. Sjöholm, R. Leino, E. Laine, D.Yu. Murzin, J. Catal. 204 (2001) 281.
[17] E. Toukoniitty, B. Ševčíková, P. Mäki-Arvela, J. Wärnå, T. Salmi, D.Yu. Murzin, J. Catal. 213 (2003) 7.
[18] Y. Orito, S. Imai, S. Niwa, J. Synth. Org. Chem. 37 (1979) 173.
[19] V.B. Shukala, P.R. Kulkarni, World J. Microbiol. Biotechnol. 16 (2000) 499.
[20] A. Lindholm, P. Mäki-Arvela, E. Toukoniitty, T.A. Pakkanen, J.T. Hirvi, T. Salmi, D.Yu. Murzin, R. Sjöholm, R. Leino, J. Chem. Soc., Perkin Trans. 1 (2002) 2605.
[21] E. Toukoniitty, P. Mäki-Arvela, R. Sjöholm, R. Leino, R. Salmi, T. Salmi, D.Yu. Murzin, React. Kinet. Catal. Lett. 75 (2002) 21.
[22] H.-U. Blaser, H.-P. Jalett, D.M. Monti, A. Baiker, J.T. Wehrli, in: R.K. Grasselli, A.W. Sleight (Eds.), Structure-Activity and Selectivity Relationship in Heterogeneous Catalysis, Elsevier, Amsterdam, 1991, p. 147.
[23] E. Toukoniitty, I. Busygin, R. Leino, D.Yu. Murzin, J. Catal. 227 (2004) 210.
[24] W.-R. Huck, T. Burgi, T. Mallat, A. Baiker, J. Catal. 219 (2003) 41.
[25] R. Hess, A. Vargas, T. Mallat, T. Burgi, A. Baiker, J. Catal. 222 (2004) 117.
[26] O.J. Sonderegger, G.M.-W. Ho, T. Bürgi, A. Baiker, J. Mol. Catal. A: Chem. 229 (2005) 19.

[27] S. Diezi, T. Mallat, A. Szabo, A. Baiker, J. Catal. 228 (2004) 162.
[28] A. Marinas, T. Mallat, A. Baiker, J. Catal. 221 (2004) 666.
[29] H.-U. Blaser, H.P. Jalett, D. Monti, J.F. Reber, J.T. Wehrli, Stud. Surf. Sci. Catal. 41 (1988) 153.
[30] E. Toukoniitty, P. Mäki-Arvela, J. Kuusisto, V. Nieminen, J. Päivärinta, M. Hotokka, T. Salmi, D.Yu. Murzin, J. Mol. Catal. A: Chem. 192 (2003) 135.
[31] M. Schürch, O. Schwalm, T. Mallat, J. Weber, A. Baiker, J. Catal. 169 (1997) 275.
[32] M. von Arx, T. Bürgi, T. Mallat, A. Baiker, Chem. Eur. J. 8 (2002) 1430.
[33] T. Bürgi, A. Baiker, J. Am. Chem. Soc. 120 (1998) 12920.
[34] M. Bártok, K. Felföldi, B. Török, T. Bártok, Chem. Commun. (1998) 2605.
[35] D. Ferri, T. Bürgi, A. Baiker, J. Chem. Soc., Perkin Trans. 2 (1999) 1305.
[36] G.D.H. Dijkstra, R.M. Kellog, H. Wynberg, J. Org. Chem. 55 (1990) 6121.
[37] D. Ferri, T. Bürgi, J. Am. Chem. Soc. 123 (2001) 12074.
[38] J. Kubota, F. Zaera, J. Am. Chem. Soc. 123 (2001) 11115.
[39] R.J. LeBlanc, W. Chu, C.T. Williams, J. Mol. Catal. A: Chem. 212 (2004) 277.
[40] A.F. Carley, M.K. Rajumon, M.W. Roberts, P.B. Wells, J. Chem. Soc., Faraday Trans. 91 (1995) 2167.
[41] Z. Ma, I. Lee, J. Kubota, F. Zaera, J. Mol. Catal. A: Chem. 216 (2004) 199.
[42] E. Toukoniitty, V. Nieminen, A. Taskinen, J. Päiväinta, M. Hotokka, D.Yu. Murzin, J. Catal. 224 (2004) 326.