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Asymmetric hydrogenation of 1-phenylpropane-1,2-dione over cinchona-modified Pt: Role of the C-9 OH group of cinchonidine

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Abstract

1-Phenylpropane-1,2-dione was hydrogenated over chirally modified 5% Pt/Al_2O_3 catalyst at 10 bar H_2 and 15 °C using toluene and acetic acid as solvents. The highest enantiomeric excess for the major product (*R*)-1-hydroxy-1-phenyl-2-propanone (*ee* = 57%) was obtained using cinchonidine as the chiral modifier. The presence of the hydroxyl group in the C-9 position of the modifier was important for achieving high enantioselectivity. When the C-9 hydroxyl group of cinchonidine was replaced by a methoxy group enantioselectivity was lost and a small 2% excess of (*S*)-1-hydroxy-1-phenyl-2-propanone enantiomer was observed. In acetic acid the reaction with cinchonidine proceeded yielding a 7% excess of the (*R*)-product. Hydrogenation of the intermediate hydroxyketones in acetic acid using cinchonidine or 9-methoxy-10,11-dihydrocinchonidine as chiral modifiers gave the corresponding (1*S*,2*R*)-diol in 67 and 78% enantiomeric excesses, respectively. By changing the solvent from acetic acid to toluene, an inversion of enantioselectivity took place yielding the (1*R*,2*S*)-diol as the main product in 38% *ee*. A mechanism was proposed involving a two-step cycle (reactant–modifier) and a three-step cycle (reactant-modified acetic acid) in order to account for the observed enantioselectivities.

Keywords: 1-Phenylpropane-1,2-dione; Asymmetric hydrogenation; Diols; Cinchonidine

1. Introduction

Enantioselective hydrogenation of activated ketones over cinchona alkaloid-modified Pt has been studied extensively [1] and the reaction mechanism has been investigated in detail. Based on the earlier experimental evidence, the C-9 hydroxyl group of cinchonidine (CD) (Fig. 1) was considered not to be important in the enantiodifferentiating step. The present mechanistic models for hydrogenation of activated ketones [1,2] do not include any interaction of the C-9 hydroxyl group of the modifier with the substrate (Fig. 1),

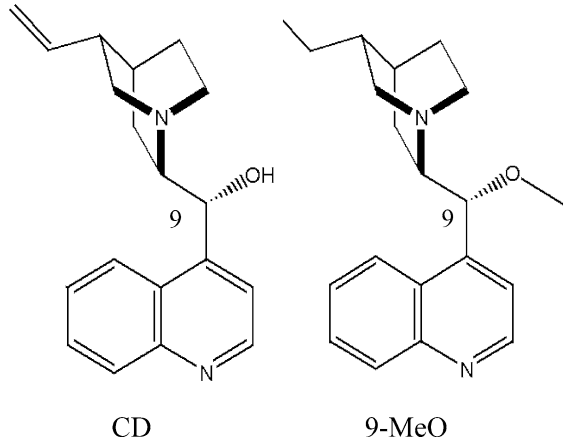

Fig. 1. Cinchonidine (CD) and 9-methoxy-10,11-dihydrocinchonidine (9-MeO).

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with the exception of the model of Augustine et al. [3]. Notably, in these reactions, an overall rate acceleration induced by the presence of the chiral modifier is typically observed. In contrast, the C-9 hydroxyl group appears to be crucial for enantioselectivity in the hydrogenation of C=C bonds over cinchona-modified Pd catalysts where the 9-methoxy-substituted analogue is ineffective as a modifier [4]. Characteristic for all Pd/CD systems is a considerable rate deceleration in the presence of a modifier.

In the hydrogenation of substituted acetophenones [5] the C-9 hydroxyl group likewise influences the enantioselectivity. The replacement of the hydroxyl group of cinchonidine by a methoxy group resulted in an inversion of enantioselectivity. Furthermore, in these reactions, the rate was lower in the presence of a chiral modifier.

1-Phenylpropane-1,2-dione can be considered as an activated diketone and is readily hydrogenated enantioselectively over cinchonidine-modified Pt catalysts. At maximum chemical yield, the enantiomeric excess (*ee*) of the main product approaches 65%, which can be further increased to $> 90\%$ by kinetic resolution [6,7]. The two reacting carbonyl groups produce upon hydrogenation four hydroxyketones and four diols (Fig. 2), thus making the reaction inherently complex. The intermediate hydrogenation product (*R*)-1-hydroxy-1-phenyl-2-propanone is utilized in the synthesis of (1*R*,2*S*)-ephedrine [8].

In addition to 1-phenylpropane-1,2-dione, hydrogenation of other diketones has been studied including butane-2,3-dione [9,10], hexane-3,4-dione [9], and cyclohexane-1,2-dione [11]. The effect of replacing the C-9 hydroxyl group with methoxy group has not been studied in diketone hydrogenation. Previously, it has been reported that with 9-*O*-(trimethylsilyl)cinchonidine as the chiral modifier the *ee* reduced from 55% to nearly zero [12]; however, the result was attributed to the bulkiness of C-9 substituent, in analogy to ethyl pyruvate hydrogenation [13]. The reaction mechanism of the hydrogenation of vicinal diketones is not completely understood. It has been proposed [9,11] that vicinal diketones would require the s-*trans* conformation to react enantioselectively to hydroxyketones; however, this was recently challenged by ab initio calculations carried out with protonated CDH^+ and **A** [14]. In α-keto ester hydrogenation the hydroxyl group of cinchonidine can be replaced by a methoxy group without any loss of *ee* [13]. The aim of the present study was to investigate the role of the C-9 hydroxyl group of the chiral modifier in the hydrogenation of 1-phenylpropane-1,2-dione (**A**) in toluene and acetic acid solution.

2. Experimental

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 2.5 nm, and dispersion 40% (H_2 chemisorption), the mean catalyst particle size 18.2 μm (Malvern)). Catalyst characterization has been described in detail previously [15,16].

1-Phenylpropane-1,2-dione (Aldrich, 22303-4, 99%) was vacuum-distilled before use, whereas toluene (J.T. Baker, 8077, $> 99.5\%$), acetic acid (J.T. Baker, 6052, 99.9%), and cinchonidine (Fluka, 27350, 98%) were used as received.

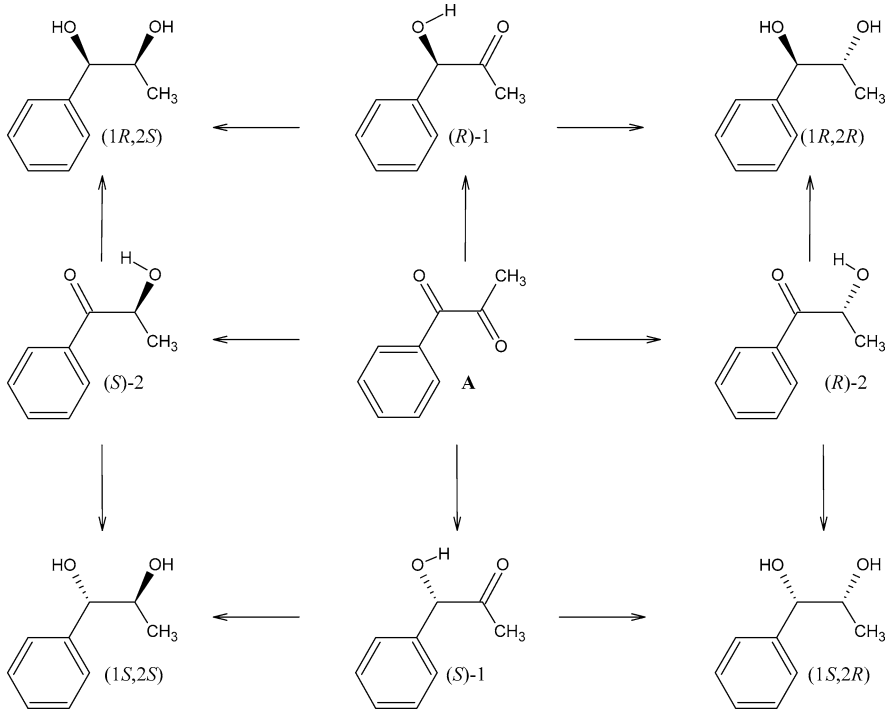

Fig. 2. The reaction scheme of 1-phenylpropane-1,2-dione (**A**) hydrogenation.

Details for the synthesis of 9-methoxy-10,11-dihydrocinchonidine can be found elsewhere [17].

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 speed 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 followed by 30 min of flushing with Ar (50 cm^3/min). The preactivated catalyst could be stored under air a minimum of 3 days without loss of activity or selectivity. The start-up procedure was as follows: the preactivated catalyst and solvent (50 cm^3) containing dissolved modifier (3.4×10^{-5} mol, which 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. The initial concentrations of **A** and modifier were 0.05 and 3.4×10^{-4} mol dm^{-3}, respectively.

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 [6].

For definitions of the selectivities, enantiomeric excess of (*R*)-1-hydroxy-1-phenyl-2-propanones is defined:

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

The enantiomeric excess ee_{RS} is defined in analogous manner using concentrations of (1*R*,2*S*) and (1*S*,2*R*). The diol selectivity S_i, e.g., for (1*S*,2*R*)-diol, has been defined accordingly

$$S_{SR} = \frac{[1S,2R]}{[1S,2S] + [1R,2R] + [1R,2S] + [1S,2R]} \times 100\%.$$

The regioselectivity (*rs*) is given by

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

3. Results

Two modifiers, cinchonidine (CD) and 9-methoxy-10,11-dihydrocinchonidine (9-MeO), were used in the present work. The CD vinyl group is hydrogenated under the employed reaction conditions during the first minutes converting it to 10,11-dihydrocinchonidine (GC-MS confirmation). Furthermore, in ethyl and methyl pyruvate hydrogenation the 10,11-dihydrocinchonidine and cinchonidine behave similarly, indicating that hydrogenation of the vinyl group has only a marginal influence [13,18]. Thus, the utilized 9-MeO and CD can be used to evaluate the influence of the C-9 hydroxyl group.

3.1. First hydrogenation step

Both modifiers decreased the reaction rate with respect to racemic hydrogenation (Table 1) and the activity could not be correlated with the enantioselectivity. This is in accordance with previous observations [7] that CD does not induce an overall rate acceleration in the hydrogenation of **A** but a slight rate deceleration. The modifier-induced rate deceleration is an opposite phenomenon to that observed in the hydrogenation of other α-functionalized ketones [1]. This indicates that some features of hydrogenation mechanisms are different for the two classes of ketones.

Regioselectivity (*rs*) varied slightly (Table 1). The highest $rs = 4.5$ was obtained with CD in toluene and with 9-MeO in acetic acid. With 9-MeO in toluene a lower rs than in racemic hydrogenation was observed indicating that this modifier promotes the reduction of the C2 carbonyl group.

By replacing the C-9 hydroxyl of CD with a methoxy group (9-MeO) the enantioselectivity, $ee_{(R)\text{-}1}$, was practically lost and a very small excess of the (*S*)-enantiomer was formed instead of the (*R*)-enantiomer. More specifically, the $ee_{(R)\text{-}1}$ decreased from 57% (*R*) to 2% (*S*) in toluene (Fig. 3). Due to the low 2% $ee_{(R)\text{-}1}$ of (*S*) it cannot be confirmed unequivocally that this would be an indication of inversion of enantioselectivity as was the case in the hydrogenation of substituted acetophenones [5]. Nevertheless, this is an important observation regarding the reaction mechanism and indicates that the C-9 hydroxyl group is involved in the enantiodifferentiating interaction between the substrate **A** and the

Table 1
The initial reaction rate, enantiomeric excess *ee*, and product distribution of diols

Modifier	Solvent	Initial rate[a]	rs[b]	$ee_{(R)\text{-}1}$[b] (%)	$ee_{(R)\text{-}2}$[b] (%)	S_{RR+SS} (%)	S_{RS} (%)	S_{SR} (%)	ee_{RS} (%)
–	Toluene	21.2	4.1	0	0	17	41	42	−1[d]
CD	Toluene	18.6	4.5	57	12	19	56	25	38
CD	Acetic acid	13.5	4.1	7	12	–	16	84	−67[d]
9-MeO	Toluene	16.8	2.7	−2[c]	3	18	41	41	0
9-MeO	Acetic acid	18.6	4.5	−2[c]	28	–	11	89	−78[d]

[a] 10^{-4} mol min^{-1} g_{cat}^{-1}.
[b] At 50% conversion of **A**.
[c] The excess enantiomer was (*S*)-1.
[d] The excess enantiomer was (1*S*,2*R*).

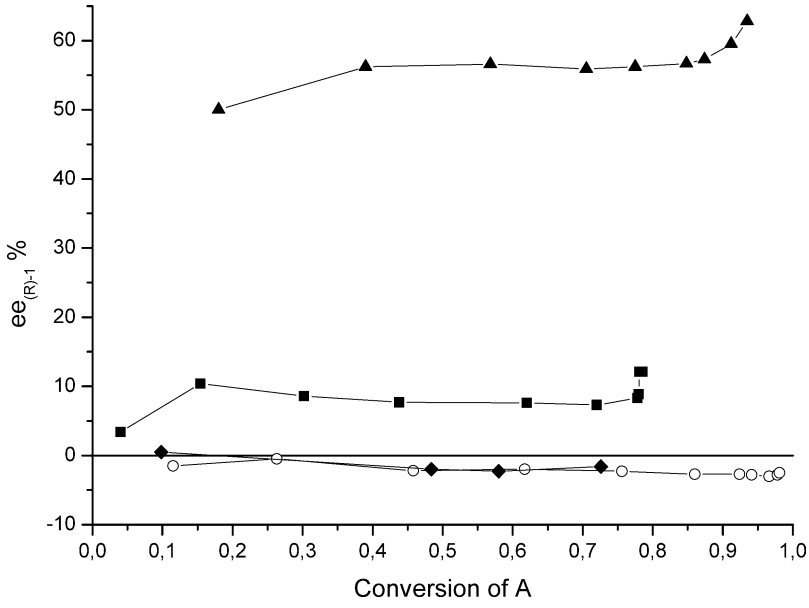

Fig. 3. The $ee_{(R)\text{-}1}$ as a function of reactant conversion. (▲) CD in toluene, (○) 9-MeO in toluene, (■) CD in acetic acid, and (◆) 9-MeO in acetic acid.

modifier. To our knowledge, similar effects have not been observed in the hydrogenation of activated C=O double bonds. However, an analogous effect has been documented in the Pd-catalyzed C=C double bond hydrogenation [4] and in the Pt-catalyzed hydrogenation of nonactivated C=O double bonds of substituted acetophenones [5].

The $ee_{(R)\text{-}2}$ displayed in Table 1 does not depend in a similar way on the modifier structure and solvent as $ee_{(R)\text{-}1}$. With CD both in toluene and in acetic acid a low 12% $ee_{(R)\text{-}2}$ was observed. Previously a 25% $ee_{(R)\text{-}2}$ was reported in toluene over CD [14], which is higher than obtained in the present work. Although there are some differences in the experimental conditions (catalyst modification procedure and H_2 pressure), a possible explanation for the difference in *ee* is, as noted in [14], the deterioration of GC column ability to separate (*R*)- and (*S*)-2 with prolonged operation time. 9-MeO exhibits a pronounced solvent effect: the negligible $ee_{(R)\text{-}2}$ of 3% in toluene increased to 28% in acetic acid. The difference in $ee_{(R)\text{-}1}$ and $ee_{(R)\text{-}2}$ dependence on solvent and on modifier structure indicates that enantioselective reactions of C1 and C2 carbonyl groups might not proceed via the same substrate–modifier complexes. Very little experimental data available about the kinetics of C2 carbonyl group hydrogenation with respect to $ee_{(R)\text{-}2}$ prevent further elaboration on the differences in the reactions of C1 and C2 carbonyl groups.

The solvent employed plays an important role and the observed *ee* is strongly dependent on the solvent polarity [19] in the hydrogenation of **A** with CD-modified catalysts. The highest enantiomeric excesses at maximum yield, $ee_{(R)\text{-}1} = 65$ and 62%, are obtained in toluene and ethyl acetate [19], respectively. The use of alcohol solvents such as ethanol ($ee_{(R)\text{-}1} = 12\%$) and methanol ($ee_{(R)\text{-}1} = 4\%$) resulted in low $ee_{(R)\text{-}1}$. Polar solvents decreased $ee_{(R)\text{-}1}$ but inversion of *ee* could not be observed [19]. In acetic acid CD modifier results in a small 7% $ee_{(R)\text{-}1}$. In previous experiments with CD in acetic acid the *ee* varied between 5 and 10% (*R*) [14]. The product distribution obtained with both CD and 9-MeO in acetic acid is similar, indicating that the reactions proceed by a similar mechanism. The product distribution for 9-MeO in acetic acid is displayed in Table 2 as a function of reactant conversion. Furthermore, this indicates that substrate–modifier interactions, which do not involve the C-9 hydroxyl group, dominate in acetic acid.

Table 2
Product distribution and conversion (X) of **A** over 9-MeO-modified catalysts in acetic acid

t (min)	X_A (%)	(*R*)-1[a]	(*S*)-1 [a]	(*R*)-2 [a]	(*S*)-2 [a]	(1*R*,2*S*) [a]	(1*S*,2*R*) [a]
5	9.7	3.9	3.9	1.2	0.7	0	0
15	48	19.4	20.2	5.6	3.1	0	0
45	83	33.6	31.6	8.6	5.1	0.4	3.4
110	86	33.2	29.0	9.0	5.2	1.0	8.9
200	88	30.9	24.2	8.3	5.0	2.4	16.8

[a] Dimensionless concentration (%), $c/c^0 \times 100\%$, $c^0 = 0.05$ mol dm^{-3}.

3.2. Second hydrogenation step

The final hydrogenation products composed of four diols (Fig. 1), i.e., (1*R*,2*S*), (1*S*,2*R*), (1*R*,2*R*), and (1*S*,2*S*). The diol distribution varied depending on the modifier and solvent employed. The (1*R*,2*R*) and (1*S*,2*S*) diols could not be separated completely and therefore in Table 1 only their sum is reported. The diol selectivity was constant with increasing conversion under reaction times used in the present work (yield of diols < 30%).

In toluene the selectivity toward (1*R*,2*R*) + (1*S*,2*S*) diols was practically constant, about 20%, and independent of the modifier used (Table 1). Approximately 40% (1*R*,2*S*) and 40% (1*S*,2*R*) were formed during the racemic reaction and

also when 9-MeO was used in toluene. With CD (1*R*,2*S*) was the main diol with an ee_{RS} of 38% in toluene. This ee_{RS} was a result of the 57% $ee_{(R)\text{-}1}$, which yields an excess of the (1*R*,2*S*)-diol via a practically racemic second hydrogenation step of the C2=O2 carbonyl group. Transient experiments in the batch reactor, where CD was injected during a racemic reaction after 90% conversion of **A** in toluene, resulted in about 0–5% ee_{RS}. This indicates that the hydrogenation of the intermediate hydroxyketone proceeds as a racemic reaction in toluene and that the obtained 38% ee_{RS} was in fact a result of the 57% $ee_{(R)\text{-}1}$ obtained in the first reaction step.

In acetic acid the diol distribution was very different from that observed in toluene. With 9-MeO and CD in acetic acid the main product was the opposite (1*S*,2*R*)-enantiomer having ee_{SR} of up to 78% and no (1*R*,2*R*) + (1*S*,2*S*) diols were formed. In AcOH the C-9 hydroxyl group has no significant effect on the product distribution as CD and 9-MeO result in nearly the same product ratio and similar ee_{SR}. Furthermore, as the $ee_{(R)\text{-}1}$ was negligible in acetic acid, the observed ee_{SR} is a result of enantiodifferentiation in the second hydrogenation step.

It was recently reported that the solvent polarity affects the diol distribution when CD is used as the catalyst modifier [19]. In nonpolar solvents (1*R*,2*S*) is the main diol with ee_{RS} ranging from 30 to 40% whereas with increasing polarity the selectivity toward (1*S*,2*R*) increases and the maximum ee_{SR} of approximately 30% has been observed in ethanol [19]. Acetic acid is a very suitable solvent for the specific substrate–modifier interactions resulting in the formation of the (1*S*,2*R*)-diol.

4. Discussion

Hydrogenation of **A** is a complex reaction and small changes in the modifier structure result in drastic changes in the product composition. The reactions of the C1=O1 carbonyl group, adjacent to the phenyl ring, exhibit many similarities to the hydrogenation of substituted acetophenones [5]; e.g., modified reactions are slower, C-9 hydroxyl group is important for high *ee*, and utilization of ethanol and acetic acid reduce notably the observed *ee*. The reactions of C2=O2, on the other hand, have similarities to the hydrogenation of activated ketones [1,2]; e.g., the C-9 hydroxyl group has a smaller influence on the stereochemical outcome and acetic acid has even a beneficial influence on the $ee_{(R)\text{-}2}$. The reaction of intermediate hydroxyketones to the main diols, (1*R*,2*S*) and (1*S*,2*R*), proceeds with high enantioselectivity in acetic acid and the C-9 hydroxyl group influences only to a minor extent the stereochemistry of these reactions whereas in toluene these reactions exhibit no enantiodifferentiation at all. Therefore, one can conclude that the reactions of C1=O1 and C2=O2 of **A** as well as the reactions of intermediate hydroxyketones are mechanistically different.

4.1. First hydrogenation step

Interaction of **A** with C-9 hydroxyl group of CD is crucial for high $ee_{(R)\text{-}1}$ and can be achieved in toluene. Such a reactant–modifier interaction involving protonated quinuclidine N and C-9 hydroxyl group is illustrated in Fig. 4. This represents a two-step mechanism, which involves only the modifier and the reactant (adsorbed on the catalyst surface). Observations during continuous hydrogenation [14] of **A** and from batch experiments [7] with varying CD amount reveal that as $ee_{(R)\text{-}1}$ increases the amount (formation rate) of (*R*)-1 increases and (*S*)-1 decreases with respect to racemic reaction. Therefore, assuming that the C=O group bonded to the protonated quinuclidine N reacts faster that the C=O group bonded to C-9 hydroxyl group a qualitatively correct product distribution for the first reaction step is obtained with the diastereomeric reactant–modifier complexes illustrated in Fig. 4. Furthermore, the reactant's interactions with the C-9 hydroxyl group and quinuclidine nitrogen cannot be easily realized in the s-*trans* conformation and therefore, the previously proposed requirement for **A** adopting a s-*cis* conformation [14] in reactant–modifier complex is valid.

4.2. Solvent effect

Acetic acid has a considerable influence on the reaction outcome. In acetic acid CD is protonated and adopts a predominantly open(3) conformation [20]. The decreased $ee_{(R)\text{-}1}$ can in principle be a result of changed conformational equilibrium of CD in acetic acid compared to toluene

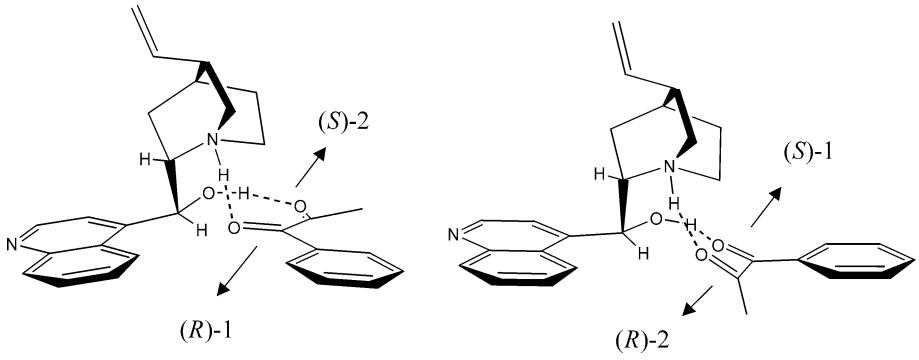

Fig. 4. Interaction of **A** with protonated CD involving the C-9 hydroxyl group of CD.

or alternatively the solvent molecules can disturb the interaction of **A** with the C-9 hydroxyl group of CD. In ethanol and methanol the $ee_{(R)\text{-}1}$ was very low, 12 and 4%, respectively [19], which is on the level of $ee_{(R)\text{-}1}$ observed in acetic acid (7%). Based on NMR measurements [21] the population of CD in open(3) conformation is very similar in toluene (70%) and ethanol (77%) and therefore, the negative solvent effect in acetic acid, is probably not due to changed conformational equilibrium of CD. Furthermore, the protonation of quinuclidine N of CD is not detrimental for enantioselectivity. In ethyl acetate with cinchonidine hydrochloride as catalyst modifier [22] a 58% $ee_{(R)\text{-}1}$ is obtained and the detrimental effect of acetic acid cannot be simply due to modifier protonation.

Von Arx et al. [23] proposed a three-step reaction mechanism involving a modifier–carboxylic acid–reactant (MAR) complex to explain the influence of carboxylic acids on hydrogenation of activated ketones. This MAR complex, as presented in [23], would effectively block the simultaneous access of **A** to the C-9 hydroxyl group and protonated quinuclidine N. According to [23] the three-step mechanism is also expected to show a reduced reaction rate due to blocking of interaction sites of the modifier by acetic acid in the case of CD, but not with 9-MeO, which has no hydroxyl group. This is in good agreement with experimental reaction rates (Table 1) as acetic acid reduces the initial reaction rate compared to toluene with CD but not with 9-MeO modifier. A plausible mechanistic explanation for the reduced $ee_{(R)\text{-}1}$ in alcoholic solvents and in acetic acid is the solvent's interaction with the C-9 hydroxyl group of CD, which prevents **A** from interacting with hydroxyl group in a mode favorable for high $ee_{(R)\text{-}1}$ as illustrated in Fig. 4. The detrimental solvent interaction can be either formation of the MAR complex in acetic acid according to the three-step mechanism [23] or hydrogen bonding of solvent molecule(s) to C-9 hydroxyl group, which prevents **A** from forming enantiodifferentiating two-step complexes in alcoholic solvents.

4.3. Diol distribution

Inversion of diol enantioselectivity from ee_{RS} to ee_{SR} took place when the solvent was changed from toluene to acetic acid. The latter favors the high selectivity toward (1*S*,2*R*)-diol and up to 78% ee_{SR} could be obtained, whereas in toluene the other (1*R*,2*S*)-enantiomer was obtained in 38% ee_{RS}. Transient experiments revealed that the second hydrogenation step in toluene is nearly racemic and the 38% ee_{RS} is a result of 57% $ee_{(R)\text{-}1}$ reacting further to (1*R*,2*S*)-diol. In acetic acid the product distribution of diols was similar with both CD and 9-MeO confirming that the C-9 hydroxyl group is not directly involved in the reactant–modifier interactions in the second hydrogenation step. However, as indicated by the high $ee_{SR} = 78\%$, there are notable reactant–modifier interactions, which require the presence of acetic acid. In acetic acid the intermediate hydroxyketone composition (i.e., (*R*)-1, (*S*)-1, (*R*)-2, and (*S*)-2, Fig. 2) is practically racemic (Table 1) and therefore, the high ee_{SR} is due to the enantiodifferentiation in the second hydrogenation step. Such a substrate–modifier complex leading to the main (1*S*,2*R*)-diol in acetic acid is displayed in Fig. 5. The main diol can be rationalized by higher steric repulsion induced either by the OH group pointing downward as in the case of (1*S*,2*S*) and (1*R*,2) or alternatively by the phenyl ring–quinuclidine ring repulsion as in the case of (1*R*,2*S*)-diol. The beneficial role of acetic acid cannot be explained by modifier protonation based on experiments with cinchonidine hydrochloride [22] modifier. It could be that the active modifier is formed according to the three-step mech-

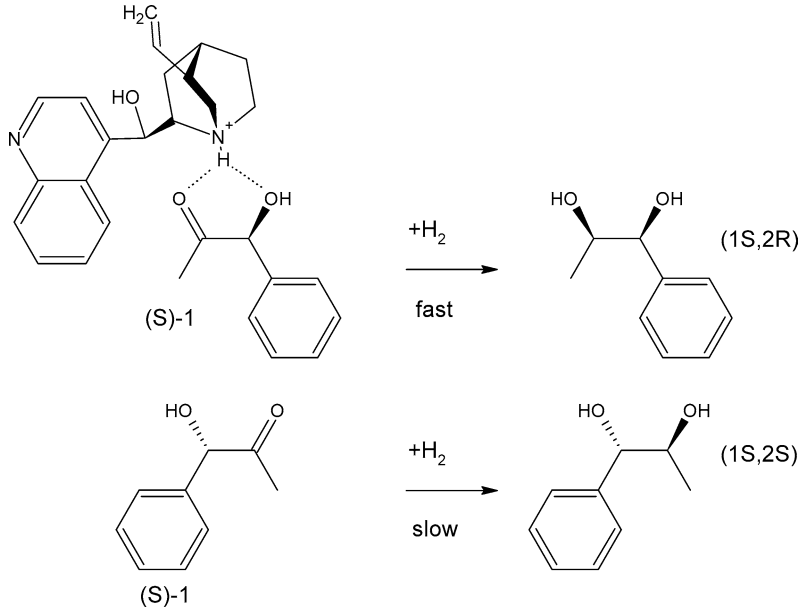

Fig. 5. Schematic illustration of the interaction of (*S*)-1 with protonated cinchonidine in open(3) conformation and the hydrogenation product.

anism [23], which first involves formation of acetic acid and modifier complex which then subsequently coordinates to hydroxyketone forming the enantiodifferentiation MAR complex on the catalyst surface. In this complex the C-9 hydroxyl group does not seem to play a significant role as both CD and 9-MeO modifier result in similar product composition in acetic acid.

5. Conclusions

Novel structure–selectivity effects, i.e., the lack of rate acceleration, the involvement of C-9 hydroxyl group in substrate–modifier interactions, and the detrimental influence of acetic acid solvent on $ee_{(R)\text{-}1}$ indicate that the hydrogenation of 1-phenylpropane-1,2-dione is different from the hydrogenation of activated ketones. High enantiomeric excess of 57% (*R*) obtained in toluene with CD results from the interactions of the reactant with the C-9 hydroxyl group of CD. The replacement of the C-9 hydroxyl group with a methoxy group resulted in a small (2%) excess of the (*S*)-enantiomer in both toluene and acetic acid.

The behavior of CD and 9-MeO was similar in acetic acid, indicating that the reactant–modifier interactions do not involve the C-9 hydroxyl group in acetic acid and lead to a small 5–10% excess of the (*R*)-enantiomer. The detrimental acetic acid effect was explained by formation of a modifier–acetic acid–reactant complex according to the three-step mechanism [23], which prevents **A** from interacting with C-9 hydroxyl group of CD and resulting in a high $ee_{(R)\text{-}1}$ according to a two-step mechanism (Fig. 4).

The solvent plays a central role in the understanding of the hydrogenation of **A** as indicated by the inversion of enantioselectivity in the final diol product from $ee_{RS} = 38\%$ to $ee_{SR} = 78\%$ by changing the solvent from toluene to acetic acid. The second hydrogenation step, hydroxyketone to diols, in toluene is practically racemic whereas in acetic acid it exhibits high enantiodifferentiation. The C-9 hydroxyl group has a negligible influence in the second hydrogenation step to (1*R*,2*S*) and (1*S*,2*R*)-diols as indicated by the similar product distribution obtained with both CD and 9-MeO modifiers.

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