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Short Communication

Hydrogenation of (*E*)-2-methyl-2-butenoic acid over cinchona-modified Pd catalyst in the presence of achiral amines: Solvent and modifier effect☆

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ABSTRACT

The effect of the solvent, modifier structure and concentration on the enantioselective hydrogenation of (*E*)-2-methyl-2-butenoic acid over Pd/Al_2O_3 modified by cinchona alkaloids was influenced by the addition of achiral amines to the reaction slurry. The solvent dependence in the presence of achiral amines showed that additives are involved in the rate determinant step of the reaction, whereas the effect of the dilution pointed to the presence of the acid dimers in the intermediate responsible for enantioselection. The dependence of the enantioselectivity on the cinchonidine concentration in the presence of amines and results obtained using cinchona derivatives and mixtures thereof were in line with our earlier assumptions related to the participation of the amine additive in the formation of the surface intermediate. Based on these and previously published results possible structures of this intermediate are suggested.

1. Introduction

Enantioselective hydrogenations are among the most useful catalytic methods for preparing optically pure chiral intermediates [1]. A large variety of chiral metal complexes have been developed and applied in asymmetric hydrogenations [2]. Recent trends of applying green and sustainable processes stimulated the development of heterogeneous catalytic systems [3]. Efficient asymmetric heterogeneous catalysts for hydrogenations were obtained by chiral surface modification of metal particles [3–5]. Among these Pd modified by cinchona alkaloids were found efficient for the enantioselective hydrogenation of unsaturated carboxylic acids [6–9]. High enantioselectivities were obtained in the hydrogenation of α-substituted cinnamic acids when achiral primary amine additives were used [8–10].

In contrast, the hydrogenation of aliphatic acids resulted in moderate optical purities, thus studies aimed at improving the stereocontrol in these hydrogenations are of great importance. Previous studies showed that achiral amines are also efficient in improving the enantioselectivities in the hydrogenation of aliphatic carboxylic acids over Pd modified by cinchonidine (CD) [11–14]. In our precious studies we have investigated the effect of the amine structure and the influence of the amines on the H_2 pressure and temperature dependence [13,14]. Based on these results it was suggested that the additive participates in the formation of the surface intermediate responsible for the chiral induction. However, further studies are needed to ascertain on the role of the additive and for the rational tuning of the catalytic system to obtain better stereocontrol of the reaction. Accordingly, we continued these studies investigating the effect of the achiral amines in various solvents and using different modifiers, earlier studied only in the absence of additives [15–19].

2. Experimental

Commercial 5% Pd/Al_2O_3 catalyst (Engelhard, 40692; [14,16]) was used as received. CD, cinchonine (CN), quinine (QN), benzylamine (BA), *N*-methylbenzylamine (MBA), (*E*)-2-methyl-2-butenoic acid (tiglic acid, TA) from Aldrich and H_2 gas (Linde AG, 99.999%) were used without purification. Cinchonidine methyl ether (CDM) and cinchonidine phenyl carbamate (CDPC) were prepared by known procedures [20,21]. Analytical grade solvents were used (in brackets the normalized empirical solvent polarity parameters, E_T^N [22]): cyclohexane (0.006), mesitylene (0.068), toluene (0.099), benzene (0.111), ethyl acetate (0.228), 2-butanone (0.327), acetone (0.355), 2-propanol (0.546), hexanol (0.559), methanol (0.762), water (1) and acetic acid (0.648).

Hydrogenations were carried out as earlier described using stainless steel autoclaves equipped with pressure transmitter for recording the pressure [13,14]. Typical reaction conditions were: 15 mg Pd/Al_2O_3, 10 cm^3 solvent, 0.05 mmol modifier, 1 mmol TA and 1 mmol amine,

☆ Dedicated to Professor Mihály Bartók on the occasion of his 80th birthday.

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5 MPa H_2 pressure, magnetic agitation (1000 rpm), 297 K, 1–2 h. Products were identified by GC–MSD analysis; quantitative analysis was carried out by GC–FID following washings with 10% aqueous HCl to remove the amine additive and the modifier. Initial rates (R_i; mmol h^{-1} g^{-1}) were calculated from the recorded H_2 pressure decrease up to 20 mol% conversion, as in previous studies [14]. Complete conversions were reached in each reaction. Enantioselectivities (enantiomeric excess, ee (%)) were calculated as: ee (%) = 100 × |[(*S*)-MBu] − [(*R*)-MBu]| / ([(*S*)-MBu] + [(*R*)-MBu]); where [(*S*)-MBu] and [(*R*)-MBu] are the concentrations of the 2-methylbutyric acid enantiomers. The reproducibility of the ee was ±2%, whereas the Ri values were reproducible within ±20 mmol h^{-1} g^{-1}, as ascertained from results of experiments repeated three times. The ee values corresponding to linear behavior with mixtures of cinchona alkaloids were calculated: ee_{calc} (%) = (R_{i1} × ee_1 + R_{i2} × ee_2) / (R_{i1} + R_{i2}); where R_{i1} and R_{i2} are the initial rates and ee_1 and ee_2 are the ees obtained with the individual modifiers.

3. Results and discussions

3.1. Solvent dependence in the presence of amine additives

Hydrogenation of TA using CD as modifier results in the excess formation of (*S*)-MBu (Scheme 1). In the hydrogenation of aliphatic unsaturated acids higher ees are obtained in apolar solvents than polar solvents [15,17]. Here we studied the effect of two achiral amines, i.e. BA and MBA, on the TA hydrogenation in various solvents (Fig. 1) and the results were compared with those obtained in the absence of amine. Results are plotted as a function of E_T^N values of the solvent, which provide a sensitive characterization of solvent polarity and has proved to give satisfactory correlations in several solvent-dependent processes [22].

Interestingly similar ees were obtained in apolar and polar solvents having E_T^N up to 0.4 (i.e. in toluene, ethyl acetate or acetone), even in the presence of amine additives only slight decrease in the ee values (within the limit of error) were observed up to 0.4 E_T^N. The lower ee in cyclohexane, (E_T^N 0.006) in the presence of both amines may be accounted for the low solubility of the acid–amine salt in this solvent. Significant and almost linear ee decrease as a function of E_T^N was detected in polar protic solvents. The lowest ees were obtained in water and acetic acid, both strong H-bond donors. Generally the use of BA or MBA increased the ee in all solvents (except acetic acid) as compared with the absence of additive. The R_i increased with the E_T^N value of the solvent, however, lower increase in presence of amine additives were obtained. These observations suggested that H-bond donor solvents (i.e. protic solvents) perturbed the efficient H-bonding between the modifier and the acid. The smaller variations of the initial rate by E_T^N in presence of amines as compared with the reactions in the absence of achiral additives (see the slope of the curves between 0.1 and 0.4 E_T^N values) indicate that the amine is involved in the rate determinant step of the reaction; otherwise the slope of the curves would be close with that observed in the absence of additives.

Although, in the hydrogenation of cinnamic acid derivatives formation of acid-modifier 1–1 complex is accepted [23–25], the surface

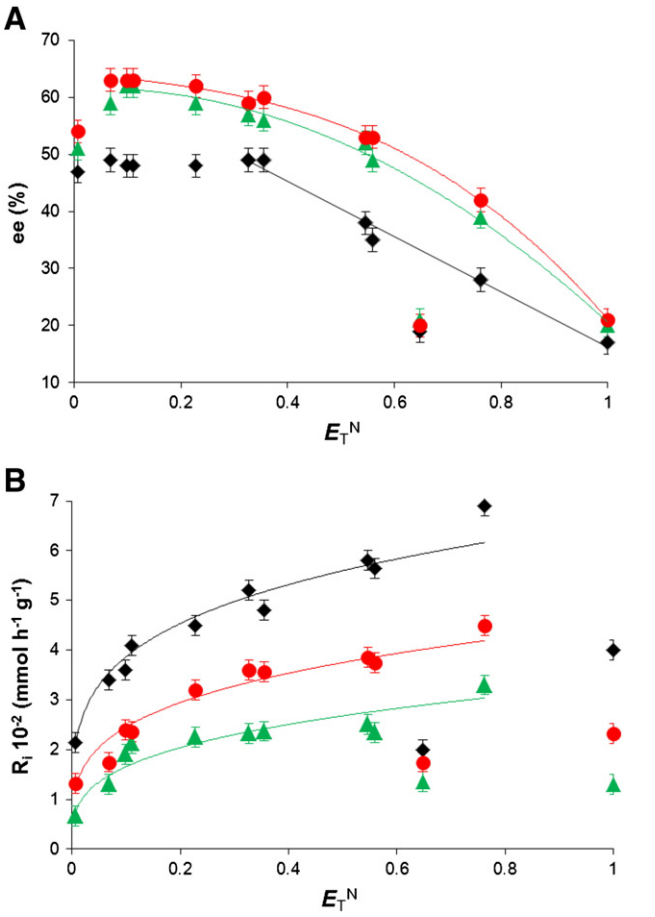
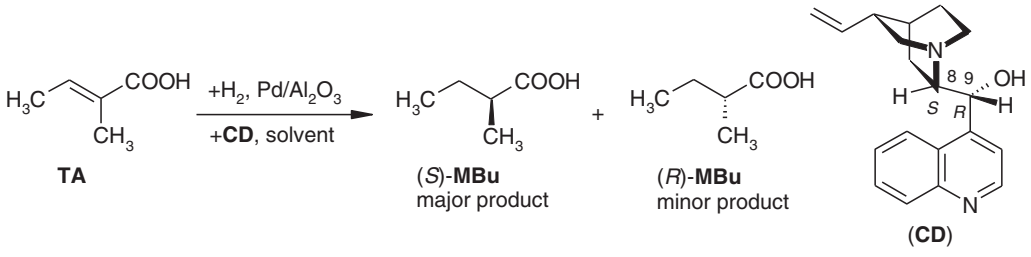


Fig. 1. Correlation between the solvent E_T^N value and the ee (A) or initial H_2 uptake rate (B) obtained in the enantioselective hydrogenation of TA using CD modifier. *Reaction conditions*: see Experimental section; in the absence of amine (♦); in the presence of BA (▲) or MBA (●).

complex responsible for enantiodifferentiation in the hydrogenation of aliphatic acids is still not well established. Formation of acid-CD complexes in 2/1 or higher ratios were suggested [15,17,26], however, 1–1 complexes were also suggested [18]. It is known that the acid monomer–dimer equilibrium and the acid–tertiary amine interactions are affected by the nature of the solvent and dilution [27,28]. Accordingly, we studied the dilution effect on the hydrogenation of TA in two solvents, i.e. toluene and methanol (Fig. 2).

Under our experimental conditions even at the lowest tiglic acid initial concentration associated dimer species should be in excess in apolar solvents, whereas in polar protic solvents the quantity of the monomer may equal that of the dimer, as shown in previous studies using acetic acid [27] or an α,β-unsaturated acid [26]. Nearly constant ees were obtained in toluene except at the lowest acid concentration, where the ee decreased significantly. Based on the decrease of the ee on increasing the toluene amount, i.e. by possible slightly shift of the



Scheme 1. Scheme of the enantioselective hydrogenation of TA over CD-modified Pd.

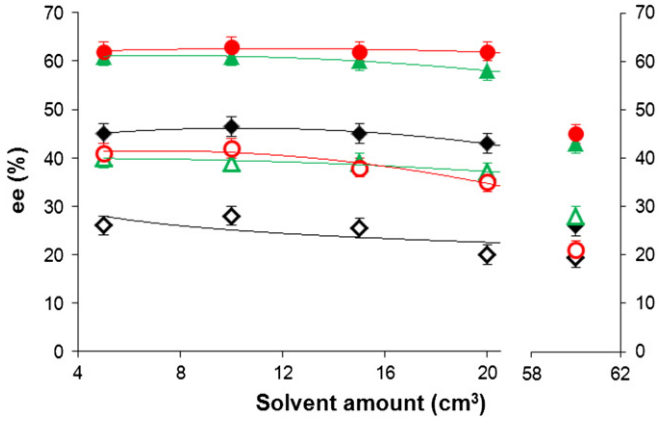


Fig. 2. The ee obtained in the enantioselective hydrogenation of TA as a function of solvent amount in toluene (closed symbols) and methanol (open symbols): without amine (♦,◊), in the presence of BA (▲,△) or MBA (●,○). *Reaction conditions*: see Experimental section.

dimer–monomer acid equilibrium in the liquid phase, one may assume that the decrease is caused by formation of CD–acid monomer intermediates, even if the liquid phase dimer/monomer ratio may be altered on the surface. Although confirmation of the composition of the surface species are still needed, according to these results it is probable that the high ee in apolar solvents is due to the interactions of acid dimers with the modifier (see Fig. 3), as shown in previous studies [16,17,26]. In methanol in the absence of additives the ee decrease was small even at the highest dilution. It is known that solvents with hydrogen-bond donor ability may interact with amine–carboxylic acid adducts [28]. Thus, formation of an associated CD–TA–HOMe surface complex incorporating methanol even under the most concentrated conditions, which is kept even under the most diluted conditions is plausible (see Fig. 3). Such an intermediate may explain both the low ee in protic solvents and the only slightly decreasing ee values obtained by increasing the dilution.

In the presence of amine additives similar decrease in the ee was observed at the highest dilution in both toluene and methanol. Accordingly, we suppose that in both types of solvents the additives act similarly, however these results could not confirm the involvement of the achiral amines in the surface intermediate responsible for enantioselection, as suggested previously.

3.2. Effect of the modifier concentration and structure

Further we attempted to ascertain on the involvement of the achiral amines in the enantiodifferentiating step by studying the effect of the CD concentration ([CD]) and the modifier structure. Such studies have been reported without using achiral amine additives [15–17] and in a recent report using epicinchonidine [29]. The effect of [CD] is presented in Fig. 4.

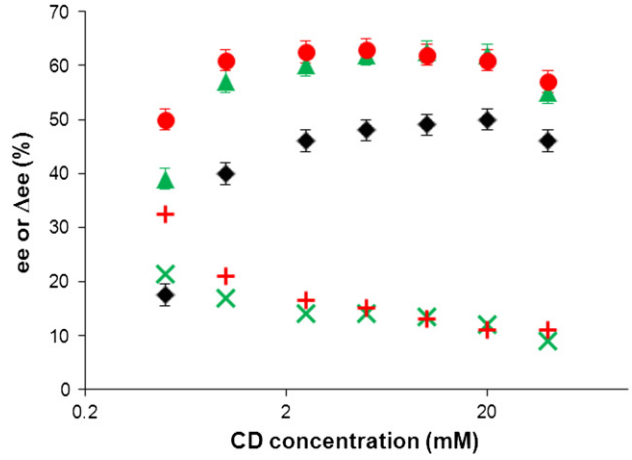
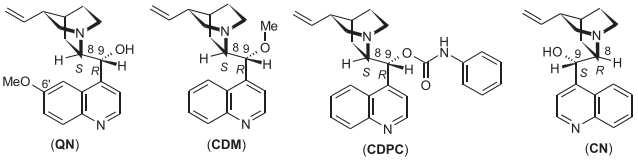


Fig. 4. Effect of CD concentration (logarithmic scale) on the ee of TA hydrogenation in absence of amine (♦), using BA (▲) or MBA (●) and on the Δee (×: $ee^{with\ BA} - ee^{without\ amine}$; +: $ee^{with\ MBA} - ee^{without\ amine}$). *Reaction conditions*: see Experimental section; solvent: 10 cm^3 toluene.

Table 1
Effect of the amine additives on the hydrogenation of TA over Pd modified by cinchona alkaloids.[a]



Entry	Modifier	Additive	R_i/t (min)[b]	ee (%) (*config.*)	Δee (%)[c]
1	CD	–	260/30	48 (*S*)	–
2	CD	BA	190/45	62 (*S*)	14
3	CD	MBA	239/30	63 (*S*)	15
4	QN	–	287/30	15 (*S*)	–
5	QN	BA	233/45	10 (*S*)	−5
6	QN	MBA	249/40	14 (*S*)	−1
7	CDM	–	548/15	25 (*S*)	–
8	CDM	BA	136/30	28 (*S*)	3
9	CDM	MBA	222/20	33 (*S*)	8
10	CDPC	–	291/35	16 (*S*)	–
11	CDPC	BA	142/45	17 (*S*)	1
12	CDPC	MBA	186/40	18 (*S*)	2
13	CN	–	270/20	39 (*R*)	–
14	CN	BA	226/30	48 (*R*)	9
15	CN	MBA	249/25	51 (*R*)	12

[a] *Reaction conditions*: see Experimental section, solvent: 10 cm^3 toluene.
[b] Initial H_2 uptake rate (mmol h^{-1} g^{-1})/reaction time.
[c] $\Delta ee = ee^{with\ amine} - ee^{without\ amine}$.

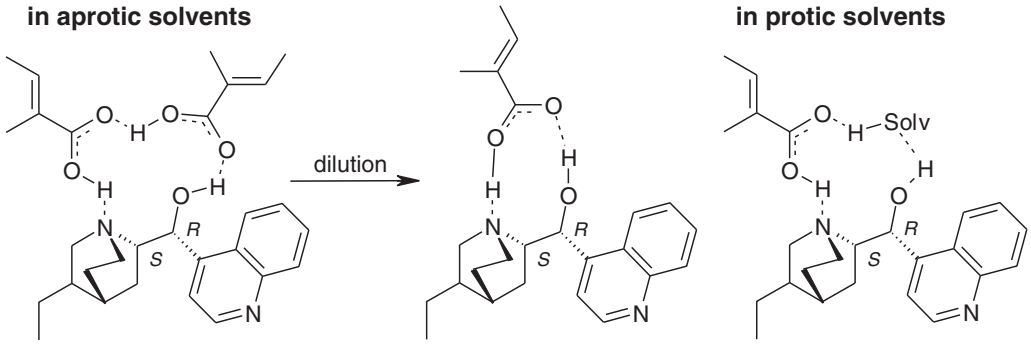


Fig. 3. Probable intermediate structures in the absence of amine additives in aprotic and protic solvents.

Table 2
Results obtained using cinchona alkaloid 1/1 mixtures as modifiers.[a]

Entry	Modifier mixture	Additive	R_i	ee (%)	ee_{calc} (%)[b]	ΔLee (%)[c]
1	CD + CN	–	230	13 (*S*)	4 (*S*)	9
2	CD + CN	BA	82	20 (*S*)	2 (*S*)	18
3	CD + CN	MBA	182	21 (*S*)	4 (*S*)	17
4	QN + CN	–	214	35 (*R*)	11 (*R*)	24
5	QN + CN	MBA	173	47 (*R*)	19 (*R*)	28
6	CDM + CN	–	371	29 (*R*)	4 (*S*)	33
7	CDM + CN	MBA	246	45 (*R*)	10 (*R*)	35

[a] *Reaction conditions*: see Table 1, 0.05 mmol modifier 1/1 mixture.
[b] ee corresponding to linear behavior.
[c] ee deviation from the linear behavior.

Higher increases in the ee in the presence of amines were obtained at low [CD] and under these conditions ([CD] 0.5 mM) the ee increase obtained by using MBA was higher than with BA (see Δee, Fig. 4). A possible explanation of the smaller effect of both achiral amines on the ee at high [CD], i.e. by increasing the modifier surface coverage, can be explained by hindered adsorption of the additive on the surface. This supports the suggestion that the amines influence the surface reaction adsorbed on the surface, i.e. possibly by participating in the formation of the intermediate responsible for the enantioselection. Results obtained over Pd modified by other cinchona derivatives are shown in Table 1.

The ees obtained with both CD and CN were strongly increased by the amine additives. In contrast the ee obtained using QN decreased in the presence of BA. Transforming the C^9–OH to methyl ether or phenyl carbamate resulted in smaller ee increase as obtained with CD, though the latter derivative bears a H-bond donor moiety. Accordingly, in the presence of either C^6- or C^9–O-substituents the beneficial effect of the additives was partially or completely lost. Taking into consideration the difference in the adsorption strengths of the aliphatic and cinnamic acid derivatives and the adsorption mode of the cinchona alkaloids over Pd [29], these observations can be rationalized by the steric hindrance of the substituents on formation of intermediates incorporating the additive, supporting the participation of the amine additive in the reacting surface intermediate.

In the hydrogenation of TA over catalyst modified by 1/1 mixtures of cinchona alkaloids (Table 2) the experimentally determined ees deviated from the calculated values corresponding to linear behavior. This non-linear phenomenon has its origin in different adsorption strengths of the intermediates formed with the adsorbed cinchona alkaloids [4,24,30,31]. The increased deviation from the linear behavior in the presence of amines should be the consequence of further increase in the difference in the adsorption strength of the intermediates in the presence of the additives. This supports the assumption that the amine participate in the formation of the surface intermediate responsible for enantioselection.

4. Conclusions

We have disclosed results obtained in the hydrogenation of (*E*)-2-methyl-2-butenoic acid over Pd modified by cinchona alkaloids supporting the involvement of the amine in the surface reaction. The solvent dependence of the ee in the presence of amines indicated that these additives are involved in the rate determinant step of the reaction. Dilution effects were in agreement with the participation of acid dimers in reactions carried out in aprotic solvents, whereas protic solvents interfere in the modifier–acid interaction. The influence of amines on

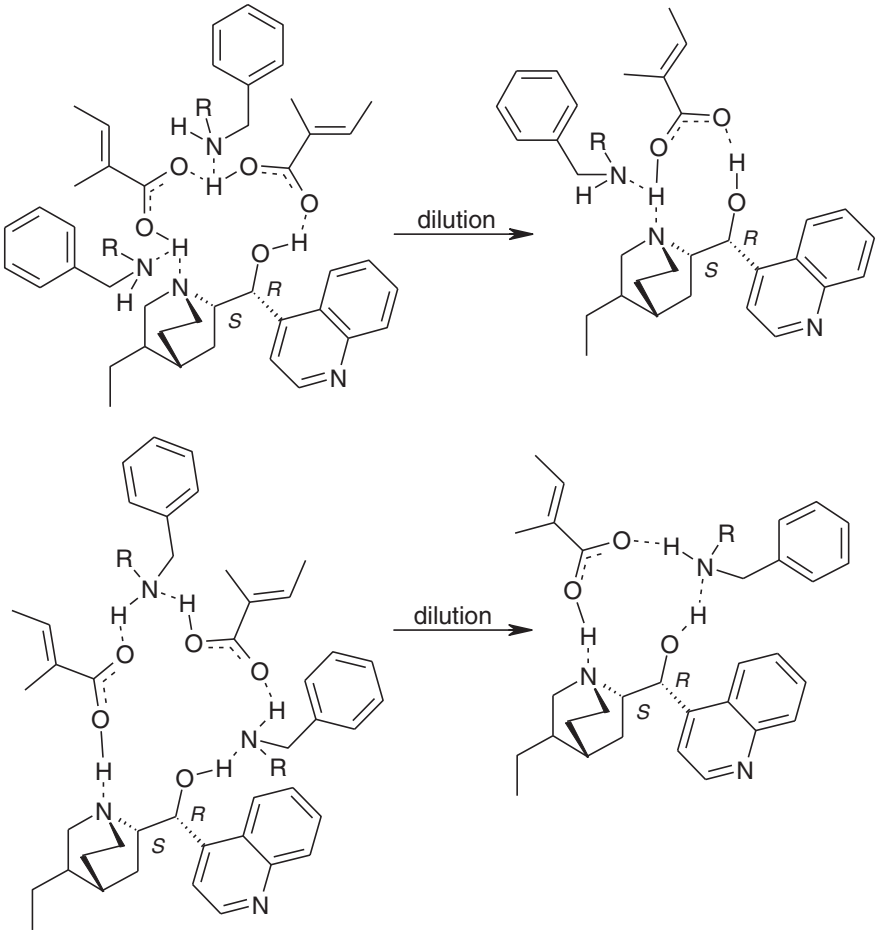


Fig. 5. Possible structures of the intermediates in the presence of amine additives in aprotic solvents.

the effect of modifier concentration showed the involvement of the adsorbed additive in the reaction possibly by participating in the formation of the intermediate responsible for the enantioselection. These suggestions were confirmed by ees obtained over catalyst modified by cinchona alkaloid derivatives and deviations from the non-linear behavior obtained using modifier 1/1 mixtures.

Based on these results combined with published data, i.e. the effect of the amine amount [14] and the structure of the intermediate in the absence of amine additives [26], we suggest structures shown in Fig. 5 as possible surface intermediate complexes formed in the presence of amine additives in aprotic solvents. According to this suggestion the possible modifier/acid/amine 1/2/2 adducts are partially transformed in 1/1/1 surface complexes by dilution resulting in weaker stereocontrol and lower ee. As was shown in Fig. 3 in protic solvents the involvement of the solvent in these interactions is probable resulting in a complex hydrogen-bonding network. Elucidation of the structure and composition of such surface species needs further studies. Although these suggestions should be further confirmed by various methods, these results represent a novel step in tailoring this catalytic system to obtain high ees in the hydrogenation of aliphatic carboxylic acids.

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