Enantioselective Hydrogenation over Cinchona-Modified Pt: The Special Role of Carboxylic Acids

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Abstract: The influence of acetic acid (AcOH) and trifluoroacetic acid (TFA) on the hydrogenation of ethyl-4,4,4-trifluoroacetoacetate has been investigated by using Pt/Al_2O_3 modified by cinchonidine and *O*-methylcinchonidine. We have shown that the sometimes dramatic changes in enantioselectivity and rate cannot simply be interpreted by protonation of the alkaloid modifier. We propose a new three-step reaction pathway, involving interaction of the carboxylic acid with the reactant and the chiral modifier. The mechanism is supported by IR spectroscopic identification of cyclic TFA–modifier ion pairs. This new approach can rationalise the poorly understood role of acids in the enantioselective hydrogenation of activated ketones over cinchona-modified platinum metals.

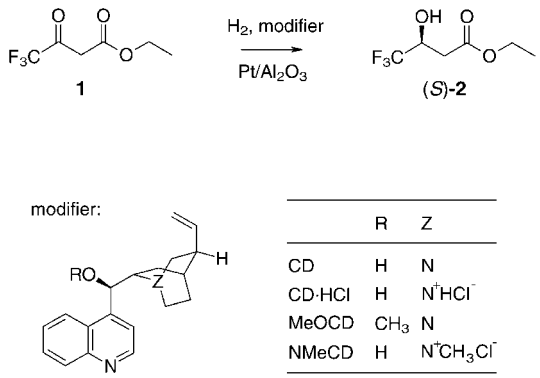
Keywords: carboxylic acids · IR spectroscopy · enantioselectivity · trifluoromethyl ketone

Introduction

Cinchona alkaloid-modified Pt, suitable for the hydrogenation of activated ketones, represents one of the most successful heterogeneous enantioselective catalysts.[1–5] In the most studied reaction, the hydrogenation of ethyl pyruvate, the influence of many reaction parameters has been investigated in detail during the past decade. It has already been recognised by Orito et al.[6] that pretreatment of a catalyst with acetic acid (AcOH) is advantageous. More recently, the best *ee* in α-ketoester hydrogenation was also achieved in AcOH.[7, 8] In the hydrogenation of α-ketoesters,[9, 10] α-ketolactones[11] and pyrrolidine triones,[12] increasing solvent polarity diminished the enantioselectivity. Only AcOH and HCOOH, which afforded good enantioselectivities, were exceptions to this negative correlation. This effect was attributed mainly to protonation of the quinuclidine N atom of cinchonidine (CD), and this information was used for the development of a mechanistic model.[13–16]

Analysis by NMR spectroscopy and theoretical calculations revealed that protonation changes the distribution of the alkaloid in various conformations in solution, favouring the so-called "open(3)" conformation (conformation in which the quinuclidine nitrogen atom points away from the quinoline ring).[17–19] Despite this progress, some aspects of the role of the acid remained unclear. Recently, it has been reported that using trifluoroacetic acid (TFA) as an additive has an even stronger effect than AcOH in the hydrogenation of ethyl pyruvate,[20] but no feasible explanation for this behaviour has been found.

In the past decade the range of application of cinchona-modified Pt has been remarkably broadened, and AcOH proven to be the most suitable solvent in the hydrogenation of α-ketoamides,[21] α-ketoacetals[22, 23] and trifluoromethyl ketones,[24, 25] providing up to 97% *ee*. This development prompted us to reinvestigate one of these reactions and to clarify the role of acids in the reaction mechanism. Compared to ethyl pyruvate, the positive effect of AcOH with respect to apolar solvents such as toluene was much more pronounced in the hydrogenation of ethyl-4,4,4-trifluoroaceto acetate.[24] We therefore chose the hydrogenation of this compound (Scheme 1) to investigate the role of AcOH and TFA.



Scheme 1. Hydrogenation of ethyl-4,4,4-trifluoroacetoacetate (**1**) over chirally modified Pt/Al_2O_3.

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In a preliminary report we proposed, based on theoretical calculations, the formation of a CD-TFA cyclic ion pair that can interact with the 4-hydroxy-6-methyl-2-pyrone reactant on the Pd surface in the enantio-differentiating step.[26] Here the catalytic experiments are supported by IR spectroscopic analysis and a general model is suggested to interpret the special role of carboxylic acids in enantioselective hydrogenation reactions over cinchona-modified metal catalysts.

Results and Discussion

Effect of AcOH in toluene: The efficiency of Pt/Al_2O_3 modified by cinchonidine (CD) or *O*-methylcinchonidine (MeOCD) in the hydrogenation of trifluoromethyl ketone (**1**) in toluene/AcOH mixtures is illustrated in Figure 1. In both

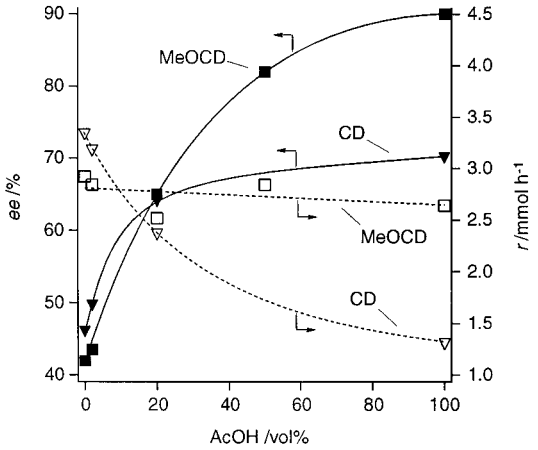

Figure 1. Hydrogenation of **1** in AcOH/toluene mixtures using CD or MeOCD as chiral modifiers. Open symbols: reaction rate (r); closed symbols: *ee*.

series the changes in enantioselectivity can be described by saturation type curves. In AcOH, MeOCD is more effective than CD, in agreement with our recent report.[24] More importantly, both modifiers provide the highest *ee* in pure AcOH. Former NMR spectroscopic studies indicated that 2 or 24 molar equivalents of AcOH were necessary to completely protonate the quinuclidine N atom of CD.[10, 27] The latter value, corresponding here to 0.2 vol% in toluene, seems to be more accurate as it is based on a comparison of the shift induced by TFA, which affords full protonation of the aliphatic N already at one molar equivalent. Independent of this difference, the curves in Figure 1 indicate that changes in the solvent properties are crucial; protonation of the quinuclidine N atom of the modifier cannot account for the whole selectivity enhancement observed.

Concerning the reaction rates (r), there is a significant difference between the two series. While the reaction rate with MeOCD was independent of the solvent composition, the rate decreased with increasing acid concentration when CD was used. This difference is attributed to a modifier–solvent interaction in which the OH group of the alkaloid is involved.

Effect of TFA in toluene: Remarkable increases in *ee* were achieved with both modifiers (15% with CD, 35% with MeOCD) by adding only 0.1 vol% of TFA; this corresponds to a TFA/modifier molar ratio of 9.6 (Figure 2). The difference between the two modifiers was larger above the optimum amount of acid: with 2 vol% TFA (TFA/CD molar ratio = 192) the enantioselectivity was almost completely lost in the presence of CD, while with MeOCD the *ee* was still better than in pure toluene.

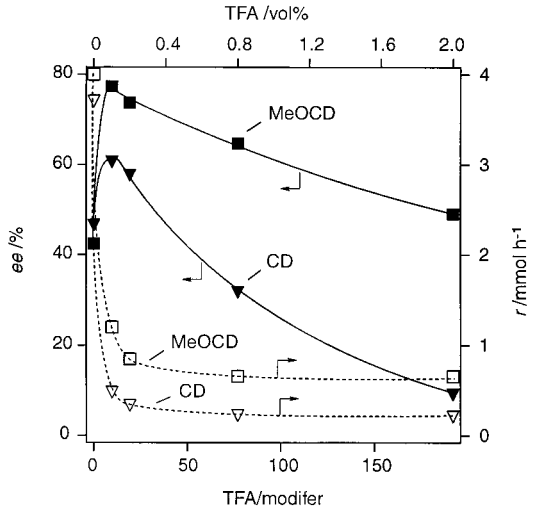

Figure 2. Hydrogenation of **1** in toluene using CD and MeOCD as chiral modifiers: changes in *ee* and reaction rate (r) upon addition of TFA. Open symbols: reaction rate; closed symbols: *ee*.

Parallel to the changes in enantioselectivity, the reaction rates dropped for both modifiers following addition of small amounts of TFA, independent of the modifier used (Figure 2). In Figure 3 the relative rates, defined as the reaction rate in the presence of TFA related to the rate in pure toluene, are compared. Over the whole concentration range, the rate deceleration induced by addition of TFA was more pronounced with CD than in the reactions with MeOCD

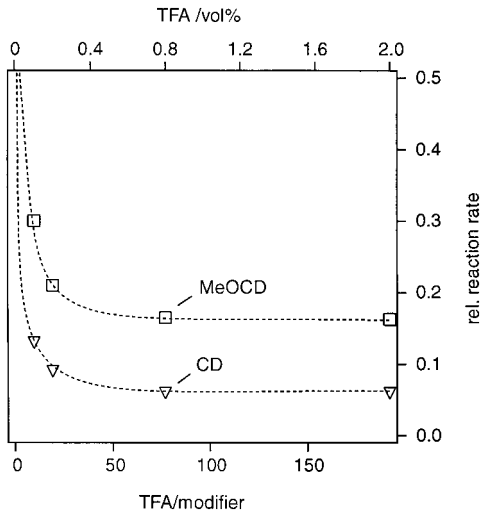

Figure 3. Hydrogenation of **1** in the presence of CD or MeOCD: comparison of the reaction rates related to the rates in pure toluene.

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(deceleration by a factor of 17 and 6, respectively). This behaviour is in qualitative agreement with the results in toluene/AcOH mixtures shown in Figure 1, where a considerable rate deceleration was observed only with CD. However, much greater amounts of AcOH are needed to obtain similar changes in *ee* and reaction rates relative to that used of TFA.

Effect of TFA in polar solvents: We have reported recently that in the hydrogenation of **1**, higher enantioselectivities can be obtained in polar solvents than in toluene.[28] For example, 70% *ee* was achieved in THF with MeOCD as modifier (Figure 4). Addition of relatively small amounts of TFA increased the *ee* to 90% although the full beneficial effect leading to 93% *ee* was obtained only at a TFA/MeOCD molar ratio of 192 (2 vol% TFA). In this solvent the *ee* did not drop at higher TFA concentration. In addition, the reaction rate did not decrease with an increasing amount of TFA as was observed in toluene (Figure 2), but remained almost constant (within ±10%).

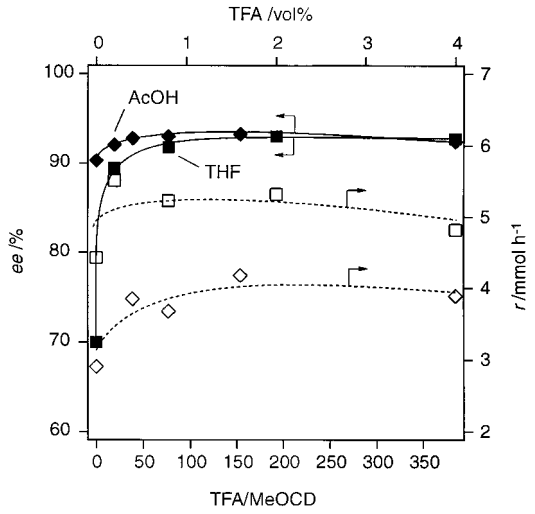

Figure 4. Hydrogenation of **1** using MeOCD as chiral modifier: changes in *ee* and reaction rate (*r*) upon addition of TFA to THF or AcOH. Open symbols: reaction rate; closed symbols: *ee*.

Addition of TFA induced a small enhancement of *ee* even in AcOH (Figure 4). Interestingly, the same maximum of 93% *ee* was achieved in both AcOH and THF. The reaction rate was practically constant in AcOH above the optimum amount of TFA.

IR spectroscopic analysis: The formation and structure of complexes between triethylamine and AcOH (existing predominantly as dimers in apolar media) were described in 1954.[29] The existence of similar TFA – modifier interactions is proven by the IR spectra in Figures 5 and 6. For comparison, the effect of increasing amount of TFA is presented for both cinchonidine (CD) and *O*-methylcinchonidine (MeOCD). The spectra contain many features similar to those reported for CD – AcOH complexes.[30] Interaction of AcOH with the quinuclidine N and the OH group of CD has been interpreted

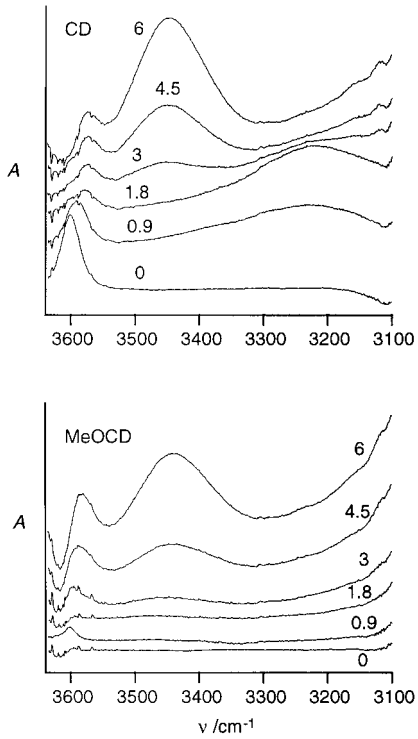

Figure 5. ν(OH) region of the IR spectra of solutions of CD and MeOCD in CH_2Cl_2 containing different amounts of TFA (TFA/modifier molar ratio between 0 and 6). Modifier concentrations are higher by a factor of 2.5 compared to the standard reaction procedure. Spectra are offset.

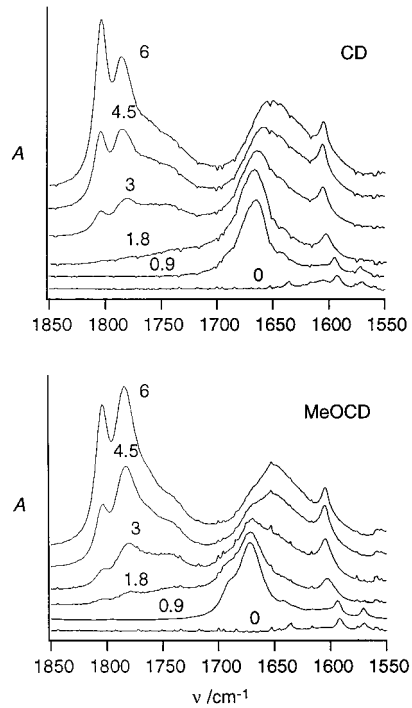

Figure 6. ν(C=O) region of the IR spectra of solutions of CD and MeOCD in CH_2Cl_2 containing different amounts of TFA (TFA/modifier molar ratio between 0 and 6). Modifier concentrations are higher by a factor of 2.5 compared to the standard reaction procedure. Spectra are offset.

by the formation of at least three types of complexes (1:1 cyclic, 2:1 cyclic and 2:1 half-cyclic). The analogous complexes for TFA and CD are depicted in Figure 7.

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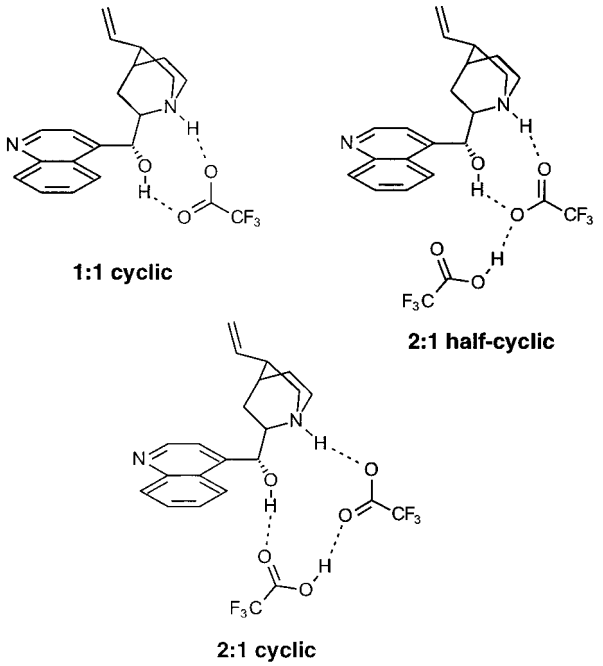

Figure 7. Structures of TFA-CD complexes (complex **A** in Figure 8) formed in solution at low TFA concentration.

The IR spectrum of CD in dichloromethane shows a peak at 3600 cm^{-1} due to the ν(OH) vibration of its non-hydrogen-bonded OH group (Figure 5). Upon addition of TFA the intensity of this band decreased and a new, broad peak at 3220 cm^{-1} appeared. The latter signal is associated with the formation of a hydrogen-bond between TFA and the OH group of CD. This observation proves that, in addition to the quinuclidine N that is protonated by one equivalent of TFA,[27] CD binds to the acid also with its OH group forming a $NH^+ \cdots OCO^- \cdots HO$ cyclic complex as shown in Figure 7. The new signals at 3575 and 3445 cm^{-1}, which appear upon further addition of TFA, belong to the hydrogen-bonded ν(OH) vibration of TFA molecules in the different CD–TFA complexes.[30] The weak ν(OH) band of the free acid[31] at 3504 cm^{-1} is obscured by these signals and can barely be detected.

In the spectra of MeOCD the signals at 3600 cm^{-1} and 3220 cm^{-1} are missing (Figure 5) because the OH group is methylated. Due to the lack of this interacting function, cyclic TFA–modifier complexes are not possible. Even so, the formation of a stable ion-pair complex (CD^+–carboxylate) by protonation of the quinuclidine N is apparent and leads to a characteristic increase of the baseline in the 3100–1900 cm^{-1} region (not shown in Figure 5). The appearance of two signals at 3580 cm^{-1} and 3440 cm^{-1} implies the formation of additional TFA–MeOCD complexes (e.g., 2:1 complexes) analogous to those formed by CD. However, due to the lack of the free OH group in MeOCD, the structural arrangement of the acid molecule(s) and MeOCD must be different from that with CD. This is reflected in the spectra, where the relative intensities of the two signals (at 3580 cm^{-1} and 3440 cm^{-1}) are different for the two modifiers.

The formation of TFA–modifier complexes is further evidenced by the spectra illustrated in Figure 6, in which the ν(C=O) region is shown. The band at 1804 cm^{-1} arises from the non-hydrogen-bonded carbonyl group of free acid molecules, while the lower frequency band at 1784 cm^{-1} can be assigned to the hydrogen-bonded carbonyl group of the acid (e.g., acid dimers). The signal at 1670 cm^{-1}, which shifts to lower frequency with increasing acid concentration, belongs to the carbonyl group of the carboxylate ion bound to the quinuclidine NH^+ group of the modifier. The shift of this band to lower frequencies is attributed to the formation of TFA–modifier complexes with molar ratios higher than 1:1.[30] All of these signals appear in the spectra of both modifiers implying that the acid molecules form complexes with both MeOCD and CD. However, the differences in the relative intensities show that the concentration of the various complexes are unequal for CD and MeOCD for the same reasons given above. Furthermore, a comparison of the region around 1800 cm^{-1} reveals that in the TFA/MeOCD mixture, with a molar ratio of 1.8, the signal for the free acid and acid dimers already appears. This is an indication that the TFA–MeOCD complexes are less stable than the TFA–CD complexes. In the latter case, at a TFA/CD molar ratio of 1.8, all acid molecules are involved in complex formation and no free acid molecules are present in solution.

It should be noted that toluene was used in the catalytic experiments (Figures 1–3), while the spectroscopic study was carried out in another weakly polar solvent, dichloromethane. This is because IR spectroscopy in toluene is difficult due to the low solubility of the modifier and the strong absorption of toluene itself. Particularly, spectroscopy of the ν(C=O) region is hampered by strong solvent absorption. In control experiments, titration of cinchonidine with TFA showed similar behaviour of the intensity of O–H vibrations in toluene as in dichloromethane. The intensity of ν(O–H) of the non-hydrogen-bonded OH group of cinchonidine decreased with increasing acid concentration, whereas the bands due to complex formation increased. The solvent had an effect, however, on the band positions. In dichloromethane, bands associated with hydrogen-bonded OH groups are observed at 3220, 3445 and 3575 cm^{-1}, whereas in toluene the corresponding bands appear at 3230, 3365 and 3530 cm^{-1}. The other possibility for "bridging" experiments is a study of the effect of carboxylic acids in the hydrogenation of **1** in a chlorinated solvent (dichloromethane or dichlorobenzene). Unfortunately, the Pt was strongly poisoned, most likely as a result of (minor) dehalogenation of the solvent.

From all of these observations we can conclude that both modifiers form stable complexes involving one or more TFA molecules, similar to those shown in Figure 7. In other words, the quinuclidine N atom of the modifier is not only protonated by TFA, but stable ion pairs exist in apolar media. In this ion pair the quinuclidine N atom (as well as the OH group of CD) is "blocked" by the acid molecule(s). Ab initio calculations indicate that the binding energy of the CD–TFA cyclic ion pair is relatively high, 23 kcal mol^{-1}.[26] Even so, no enantioselectivity would be possible if access to the modifier were prevented. The observed dramatic increase in enantioselectivity in Figures 2 and 4 implies that such a TFA–modifier complex is the real chiral modifier, affording enhanced enantioselectivities but lower reaction rates. Therefore, in the

enantio-discriminating reaction step an arrangement of reactant, chiral modifier and acid has to be considered.

Proposed reaction mechanism: The catalytic experiments and IR spectroscopic analysis indicate that hydrogenation of **1** on the Pt surface is governed by specific molecular arrangements involving the modifier, the reactant and one or more carboxylic acid molecules. We suggest a three-step reaction mechanism to interpret the rate and enantioselectivity of the hydrogenation reaction, as shown in Figure 8. In the first step

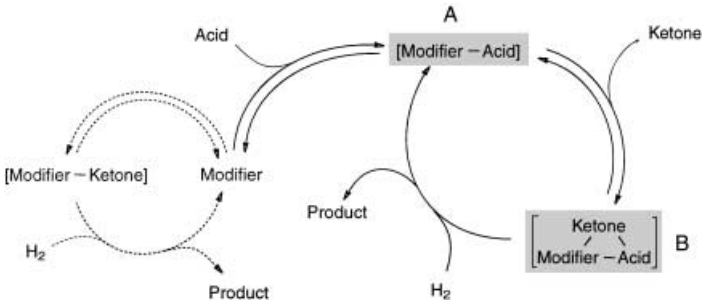

Figure 8. Three-step reaction mechanism proposed for the enantioselective hydrogenation of trifluoromethyl ketones in the presence of carboxylic acids. The presently accepted two-step reaction mechanism (valid in the absence of carboxylic acids) is indicated by dashed lines.

the chiral modifier and at least one carboxylic acid molecule form an acid–modifier complex (complex **A**) of the type shown in Figure 7. The existence of such complexes in apolar media is proven by IR spectroscopic analysis. The equilibrium of formation of complex **A** (Figure 8) depends on the strength of the acid, therefore a significant difference between AcOH ($pK_a \equiv 4.75$) and TFA ($pK_a \equiv 0.3$) is likely. Acid strength also influences the stability and structural rigidity of the alkaloid–acid complexes.

Some destabilisation of complex **A**, coupled with increasing structural flexibility, can be expected upon solvation in polar and polar protic solvents. This solvent effect facilitates the access of reactant to the possible interaction sites of **A**, which is a prerequisite for the formation of the enantio-discriminating ketone–modifier–acid complex (complex **B** in Figure 8). Upon hydrogen uptake and enantioselective transformation of the reactant, the product is released leaving complex **A**, which is involved in the next cycle, behind.

Evidently, this is not the exclusive reaction pathway. In the absence of a sufficient amount of acid the commonly accepted two-step reaction mechanism dominates. This mechanism, shown by dotted arrows in Figure 8, comprises only the modifier and reactant in the enantio-discriminating complex[16] and affords considerably lower *ee*'s in the hydrogenation of **1** (by up to 48%, see Figure 1).

Note that all these steps occur on the Pt surface (not indicated in Figure 8) on which the chiral modifier is strongly adsorbed by its aromatic ring system ("anchoring moiety").[32–36] Unfortunately, there is currently no in situ information available on the adsorption mode of modifier–reactant complex on Pt, either with or without a carboxylic acid.

Interpretation of the catalytic experiments by the three-step model

Comparison of cinchonidine (CD) and O-methylcinchonidine (MeOCD): In any solvent, addition of a carboxylic acid led to rate deceleration in the presence of CD as chiral modifier; the effect was less pronounced or even negligible with MeOCD (Figures 1–3). The *ee* increased in all experiments with both modifiers. Evidently, in the presence of AcOH or TFA protection of the hydroxyl group of CD (leading to MeOCD) is beneficial for enantioselection and for the overall reaction rate.

The main difference between the two modifiers is that MeOCD cannot form cyclic complexes with the carboxylic acids (Figure 7). The cyclic complexes, feasible only with CD, are expected to be more stable and also more rigid. For this reason coordination of a reactant molecule to the acid–modifier ion pair **A**, which is necessary for the formation of the enantio-differentiating complex **B**, is less favoured with CD; this results in lower reactivity of the acid–CD ion pair **A**. However, the lower reactivity of complex **A** is not detrimental to the enantio-differentiation. On the contrary, the three-step reaction pathway in the presence of a carboxylic acid provides higher enantioselectivities with both modifiers (Figures 1 and 2) as long as a large excess of TFA is not added.

Role of acid strength: Enhanced selectivity could be achieved with both carboxylic acids tested (Figures 1 and 2). Much smaller amounts of TFA were required to obtain similar or even more pronounced effects compared with the use of AcOH. With the stronger acid, TFA, the complex **A** is more stable and, with respect to AcOH, the modifier + acid $\Leftrightarrow$ **A** equilibrium is shifted in favour of **A**. A further advantage of TFA is its decreased tendency to form hydrogen-bonded dimers in solution.[37] At a certain concentration, the number of free acid molecules interacting with the modifier is therefore higher than when AcOH is used.

The correlation between *ee* and acid/modifier molar ratio in Figures 1 and 2 demonstrates that protonation of the quinuclidine N atom alone is not sufficient to achieve the maximum *ee*. This conclusion is supported by the results obtained with CD·HCl (Table 1). Although the quinuclidine N atom is protonated in this modifier, it is no more effective in the hydrogenation of **1** than CD.

All of these findings indicate that a stable ion pair complex (**A**) is responsible for the increased enantioselectivity. Due to the strong acidity of TFA, formation of complex **A** is favoured at low acid concentration, leading almost exclusively to product formation through the three-step reaction pathway.

Table 1. Influence of modifier structure on enantioselectivity in the hydrogenation of **1** and ethyl pyruvate in weakly polar and acidic media at standard conditions.

Compound	Solvent	CD *ee* [%]	CD·HCl *ee* [%]	MeOCD *ee* [%]	NMeCD *ee* [%]
1	toluene	46	42	43	< 2
1	AcOH	70	–	90	< 2
ethyl pyruvate	toluene	86	89	80	< 2
ethyl pyruvate	AcOH	94	–	95	< 2

The selectivity enhancement observed in this pathway is intrinsically coupled with a lower reaction rate due to "blocking" of the interaction sites of the modifier by the acid molecule(s) in **A**. The increase in *ee* by 35%, together with a drop in reaction rate by a factor of 3.5 upon addition of 9.6 equivalents of TFA (Figure 2), further suggests adherence to the three-step reaction pathway.

In contrast, a large excess of AcOH is required to effectively shift the equilibrium towards the formation of complex **A** and thus favour the three-step reaction pathway. This provides an explanation as to why the *ee* increased slowly with increasing AcOH concentration in toluene/AcOH mixtures (Figure 1). The lower stability of this complex then allows a faster coordination of the reactant and a smaller decrease in reactivity compared to reactions carried out in the presence of TFA.

Solvent effect: When the hydrogenation of **1** over MeOCD-modified Pt was carried out in polar solvents such as THF or even AcOH, higher amounts of TFA were needed to reach the maximum in *ee* and no rate deceleration was observed (Figure 4). These changes are attributed to the effect of solvation of complexes **A** and **B**. As described above, a high stability of complex **A** is needed to favour product formation following the three-step reaction pathway. Upon solvation in a polar solvent, the structural flexibility of **A** is increased significantly. For this reason the reactivity of **A** towards coordination of a reactant molecule (leading to **B**) and transformation of the reactant to the product is enhanced. As the overall reaction rate is controlled by the rate-determining ("slowest") step and formation of complex **A** is very fast, the increased reactivities of **A** and **B** in polar solvents eliminate the dramatic drop in overall reaction rate observed upon TFA addition to toluene (compare Figures 1 and 4).

The slight increase in *ee* after addition of TFA to AcOH (Figure 4) can be interpreted in terms of the effect of acid strength as discussed above. The small changes induced by TFA indicate that exchanging AcOH by TFA in complexes **A** and **B** has only a minor influence on the enantio-discrimination.

In summary, the best reaction conditions in the hydrogenation of the trifluoromethyl ketone (**1**) are those that favour product formation following the proposed three-step reaction mechanism, leading to enhanced enantioselectivities without a considerable rate deceleration. This is achieved by working in a polar solvent doped with small amounts of TFA, or in pure AcOH. Compared with CD, the use of MeOCD is also beneficial.

Possible structures of the enantio-discriminating complex B: The catalytic experiments carried out in the presence of a carboxylic acid indicated that complex **B** has sufficient conformational rigidity and structural flexibility to allow the observation of high *ee* and good reaction rates. An intriguing question is the real nature of reactant–modifier–acid interactions in complex **B**. Valuable information on the structure of **B** is provided by the hydrogenation of **1** over Pt/Al_2O_3 modified by some simple CD derivatives (Table 1). The results of the hydrogenation of ethyl pyruvate, which is the most studied reaction on chirally modified Pt, are shown for comparison. It is evident that the OH group of the modifier is not crucial in enantio-differentiation, but quaternation of the quinuclidine N atom of CD with MeI leads to a complete loss of *ee* with both reactants, independent of the solvent (toluene or AcOH). This is a strong indication that the quinuclidine N atom of the modifier interacts with the reactant in both solvents in the enantio-discriminating step. An N-H-O type interaction involving the keto-carbonyl O atom has been proposed for the hydrogenation of ethyl pyruvate,[5, 15, 16, 32] ketopantolactone[11] and trifluoroacetophenone.[38]

On the basis of these data, the open and cyclic complexes depicted in Figure 9 represent some possible structures of complex **B**. The structures **I**–**VI** illustrate possible interactions of reactant, modifier and acid without considering the adsorption on the metal surface. The complexes **I**–**V** in Figure 9 are formed from the 1:1 or 2:1 acid–CD complexes **A** (shown in Figure 7) by insertion of a reactant molecule into the cyclic structure. The complexes **I** and **III** are considered as the most probable cyclic structures when CD is used as modifier. They include an N-H-O type interaction with the reactant and an additional interaction with a carboxylic acid molecule. In complexes **II**, **IV** and **V** the OH group of CD plays a crucial role in the reactant–modifier interaction; this contradicts the experimental observations as methylation of the OH function does not hinder the enantio-differentiation (Table 1). In **II** and **III** the acid–reactant interaction is

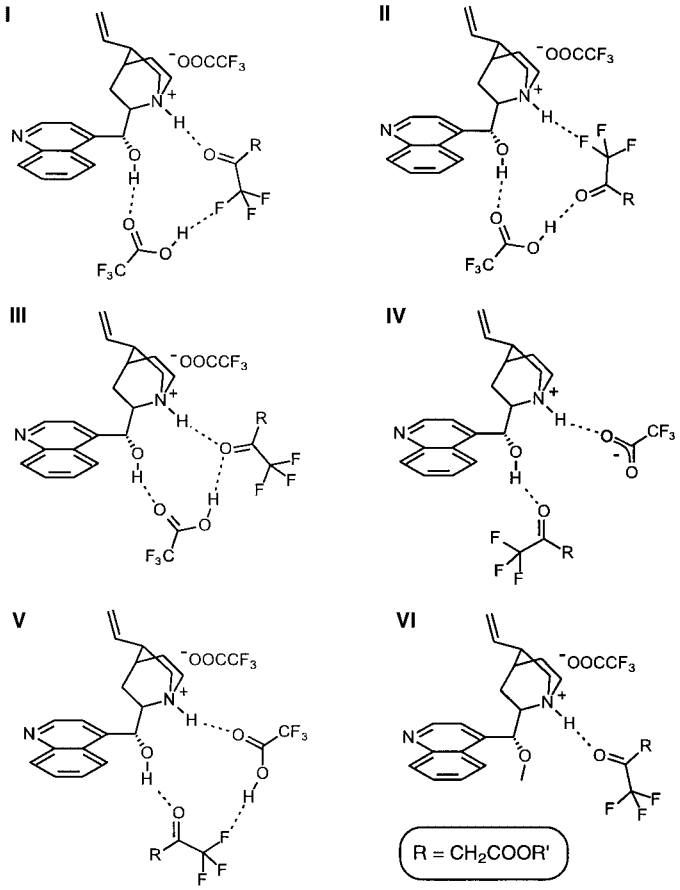

Figure 9. Possible structures of the reactant–modifier–carboxylic acid complex (complex **B** in Figure 8) responsible for enantio-discrimination (note that the interaction with the metal surface is not included).

directed from the OH group of the acid towards the carbonyl O atom of the reactant. IR spectroscopy has recently revealed that such an interaction between TFA and another trifluoromethyl ketone (2,2,2-trifluoroacetophenone)[39] is very stable in apolar media.

Complex **VI** represents a feasible interaction between the protonated MeOCD and **1**. This singly-bonded complex is expected to be less stable than the cyclic structures, but, according to the catalytic experiments, affords higher enantioselectivity (Figures 1 and 2). A possible explanation for this increased efficiency is that the energy (or reactivity) difference between the singly-bonded pro-(*S*) and pro-(*R*) complexes is bigger than in the case of the cyclic complexes. Complex **VI** may be formed with CD, but with this modifier the more stable cyclic complexes are favoured. Finally, the singly-bonded complex **VI** is not only less stable but also more reactive than the cyclic structures. This interpretation is supported by the higher reaction rates observed in the presence of MeOCD as modifier, relative to those achieved with CD-modified Pt. Note that the reactant–modifier interaction in complex **VI** is similar to that suggested for the hydrogenation of ethyl pyruvate in an acidic medium.[16]

The above interpretation may serve as a working hypothesis for future studies necessary to prove the feasibility of any of the proposed models.

Influence of the size of ester group in the reactant: Our suggestion for a three-step mechanism in the hydrogenation of **1** in acidic media is supported by the striking results obtained by using the methyl, ethyl or isopropyl esters of **1**. In an acidic medium over MeOCD-modified Pt/Al_2O_3 the *ee*'s were high with all reactants independent of the size of the ester group (92–93% in a TFA/THF mixture and 89–90% in AcOH, Figure 10). Upon replacing MeOCD by CD in AcOH,

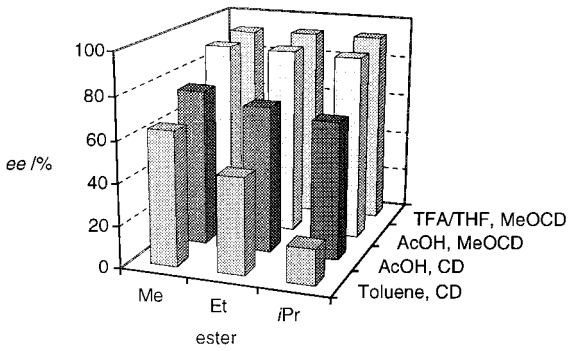

Figure 10. Enantioselectivities obtained in the hydrogenation of methyl-, ethyl- and isopropyl-4,4,4-trifluoroacetoacetate in the presence or absence of acid.

the *ee* decreased to 66–75% with increasing bulk of the ester. The loss of *ee* was even more pronounced when changing to toluene. Increasing the size of the ester group, the *ee* decreased from 64 to 17%. This is a strong indication that hydrogenation of these compounds in toluene and AcOH proceeds by two different reaction mechanisms. In AcOH the enantio-differentiation is not, or is only to a small extent, sensitive to the size of the ester group in **1**. In contrast, a structurally different complex, in which the bulkiness of the ester group is critical in the enantio-differentiating step, is formed in the absence of acid. These results support our proposal for the two-step and three-step reaction pathways in the absence or presence of a carboxylic acid, respectively (Figure 8).

Mechanistic implications for the hydrogenation of other activated ketones: As mentioned in the introduction, the enantioselectivities in the hydrogenation of α-ketoacetals, α-ketolactones, pyrrolidine triones and α-ketoesters were outstanding in acidic solvents. In the most studied reaction, the hydrogenation of ethyl pyruvate, 97% *ee* has been achieved in AcOH.[8, 40] The question arises as to whether the suggested three-step reaction mechanism is also valid for this reaction in acidic media. It has been reported that upon addition of AcOH to toluene, and TFA to toluene or AcOH, the *ee* increased significantly.[20] However, no reaction rates were reported and the enantioselectivities were far from optimum. We have also observed a strong positive effect of acid (AcOH, TFA) addition in the enantioselective hydrogenation of a pyrrolidine trione, but, again, only under conditions that were far from optimal.[41] This is an important deviation from the observations surrounding the hydrogenation of **1**.

A comparison of the hydrogenations of ethyl pyruvate and **1** in toluene containing increasing amounts of AcOH reveals some analogies as well as differences. A saturation-type curve was observed in both reactions (Figure 11). However, in the

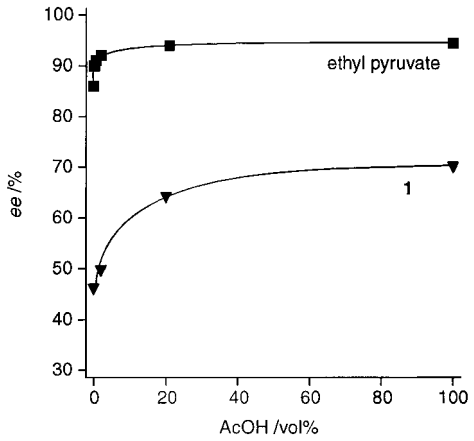

Figure 11. Comparison of the enantioselectivities in the hydrogenation of **1** and ethyl pyruvate in AcOH/toluene mixtures, using cinchonidine as chiral modifier.

hydrogenation of ethyl pyruvate about half of the positive effect was achieved already with 24 molar equivalents of AcOH, which are needed to completely protonate the quinuclidine N atom of CD,[27] and the optimum in *ee* at more than an order of magnitude higher acid concentration was only 2–3% higher. In contrast, in the hydrogenation of **1**, 24 equivalents of acid afforded only a small enhancement in *ee*.

Hydrogenation of ethyl pyruvate is almost as efficient in toluene as in AcOH, making a comparison more difficult. Although the two curves in Figure 11 are similar, the sharp initial increase of *ee* in the hydrogenation of ethyl pyruvate

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indicates that in this reaction the effect of protonation of the modifier is more important than in the hydrogenation of **1**. This being so, a spectroscopic analysis of the reactant–cinchonidine–AcOH system would be necessary to evaluate the feasibility of the three-step reaction pathway in the hydrogenation of ethyl pyruvate and other activated ketones over chirally modified Pt.

Conclusion

The long-standing question of why AcOH, used as solvent or additive in the enantioselective hydrogenation of activated ketones over chirally modified Pt, affords the highest enantioselectivities has been adressed. A systematic investigation of the role of AcOH and TFA in the hydrogenation of trifluoromethyl ketone (**1**) revealed dramatic effects on enantioselectivity and reaction rates. The results indicate that—at least in the hydrogenation of **1**—the reason for the outstanding performance of the catalytic system can be traced to the propensity of carboxylic acids to form acid–modifier ion-pair complexes. The existence of such complexes has been confirmed by IR spectroscopy. These acid–modifier ion-pair complexes are suggested to act as the real chiral modifiers over Pt. A new three-step reaction pathway, which can rationalize the behaviour of the Pt–cinchona system in the presence of carboxylic acids is proposed.

Experimental Section

The 5 wt % Pt/Al_2O_3 catalyst (Engelhard 4759, metal dispersion after heat treatment: 0.27, as determined by TEM) was pre-reduced in flowing hydrogen for 90 minutes at 400 °C. After cooling to room temperature in hydrogen, the catalyst was transferred to the reactor without exposure to air. Ethyl-4,4,4-trifluoroacetoacetate (**1**) was distilled, and THF was dried over potassium before use. All other chemicals were used as received. *O*-Methylcinchonidine (MeOCD)[42] and *N*-methylcinchonidinium chloride (NMeCD)[43] were synthesised as described previously.

Hydrogenations were carried out at room temperature (approximately 20 °C) in an autoclave equipped with a 50 mL glass liner and a PTFE cover in order to keep the system inert. Efficient magnetic stirring (1000 rpm) was applied to avoid hydrogen transport limitation in the slurry reactor. Total pressure (10 bar under standard conditions) and hydrogen uptake were controlled by computerised constant-volume constant-pressure equipment (Büchi BPC 9901). According to the general reaction procedure the catalyst (42 ± 2 mg) was added to a mixture of the modifier (6.8 μmol) and the reactant (0.34 g, 1.85 mmol) in 5 mL solvent (reactant/modifier molar ratio: 270). Conversion and enantioselectivities were determined by direct gas chromatographic analysis of the reaction mixture using a chirasil-DEX CB (Chrompack) capillary column in a HP 6890 gas chromatograph. For the hydrogenation reactions of **1**, diglyme and decane were used as internal standards in THF and toluene, respectively. Enantioselectivity is expressed as $ee\ (\%) = 100 \times |(R-S)|/(R+S)$. Average reaction rates (r) were calculated based on the time needed to obtain full conversion or, in slow reactions, based on the conversion achieved in two hours of reaction time. The estimated standard deviations are less than ± 0.5 % for *ee* and ± 5–20 % for TOF (the higher values are related to the fast reactions).

Dichloromethane (Fluka) was used as solvent for the IR spectroscopy experiments and was dried over molecular sieves (5 Å). A Bruker IFS-66 spectrometer was used at a resolution of 1 cm^{-1} and recording 200 scans. The spectra were measured in a cell equipped with CaF_2 windows with a 0.5 mm path length. The spectrum of pure dichloromethane was used as a reference.

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