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A New Reaction Pathway in the Enantioselective Hydrogenation of Activated Ketones on Cinchona-Modified Platinum

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The mechanism of the heterogenous enantioselective hydrogenation of ethyl-4,4,4-trifluoroacetoacetate has been studied in alcoholic solvents. The reaction was catalyzed by Pt/alumina modified with O-methyl-cinchonidine. Changes in reaction rate, ee, and composition in solution were followed during reaction, using kinetic analyses and NMR. The conversion dependence of ee and the effect of preequilibration of the reaction mixture are attributed to the competing hydrogenation of the keto-carbonyl group and the hydrogenolysis of the C–OR bond of the racemic hemiketal formed. We propose that the reaction route via the hemiketal is important because the hemiketal/keto molar ratio is high (up to ca. 500 after equilibration) and the hemiketal possesses sufficient reactivity toward hydrogenolysis over Pt. This reaction pathway is less important in the enantioselective hydrogenation of ethyl pyruvate, an activated ketone often used as a model reactant.

Key Words: **heterogeneous; enantioselective; hydrogenation; trifluoromethyl ketone; ethyl pyruvate; Pt/alumina; O-methyl-cinchonidine; hemiketal; alcohols; NMR; mechanism.**

INTRODUCTION

Enantioselective hydrogenation over chirally modified metals, such as the Pt-cinchona (1–7), Ni-tartaric acid (8–10), Pd-cinchona (11–13), and Pd-vinca alkaloid (14) systems, represent technically simple and inexpensive solutions to asymmetric synthesis. The application range of the Pt-cinchona alkaloid system, discovered by Orito *et al.* (15, 16), for the hydrogenation of α-ketoesters, has been broadened remarkably in recent years (17–19). The successful hydrogenation of an α,α,α-trifluoromethyl ketone (trifluoroacetophenone (20, 21)), and recently some α-ketoacetals (22, 23), demonstrate that the crucial requirement the reactant has to fulfill is the presence of an electron-withdrawing group in α-position to the keto-carbonyl group. The role of the activating function in the mechanism of enantioselection is not completely understood.

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The remarkably different mechanistic models suggested by various research groups to rationalize the observed enantio-differentiation agree in the point that the chiral modifier interacts on the Pt surface with the keto-carbonyl function of the reactant (3, 6, 24, 25). The enol being always present in equilibrium with the ketone is considered to be a spectator species on Pt (26, 27).

We have recently reported (28) the facile hydrogenation of α,α,α-trifluoro-β-ketoester **1** to the corresponding β-hydroxyester **2** (Scheme 1). Pt/alumina modified with O-methyl-cinchonidine (MeOCD) afforded 90% ee to (*S*)-**2** in AcOH. Interestingly, water had a big impact on this reaction via formation and subsequent hydrogenolysis of the hydrate of **1**. In the presence of even small amounts of water the product distribution is controlled by the simultaneous hydrogenation of the equilibrated carbonyl and hydrate forms of **1**, though the reactivity of the latter species is much lower. As the two species afford the opposite enantiomers in excess, the competing reaction pathways can rationalize the observed inversion of ee during reaction (29).

Another possible competing reaction pathway is the formation of hemiketals from activated ketones in alcoholic solvents and the subsequent hydrogenolysis of the ether bond. The rate and extension of hemiketal formation depends on the chemical structure of the reactant and the alcohol. In the hydrogenation of ethyl pyruvate the ee varied randomly with the structure of alcoholic solvents, thus a significant contribution of this route to the product distribution was excluded (30). It has been reviewed recently that in C–O bond hydrogenolysis the reactivity of C–OR functions is higher than that of C–OH groups (31). Hydrogenolysis of a cyclic intramolecular hemiketal of a β-ketoester has been achieved with Pt in ethyl acetate, though the reaction required high Pt/reactant ratio and 20–22 h at room temperature (32, 33). Under similar conditions, Pd/C was efficient in the hydrogenolysis of a cyclic ketal of a terpenoid to the corresponding alcohol (34).

Here we report the first evidence for hydrogenolysis of the hemiketal of an activated ketone (**1**) in alcoholic solvents as a major reaction pathway over cinchona-modified Pt.

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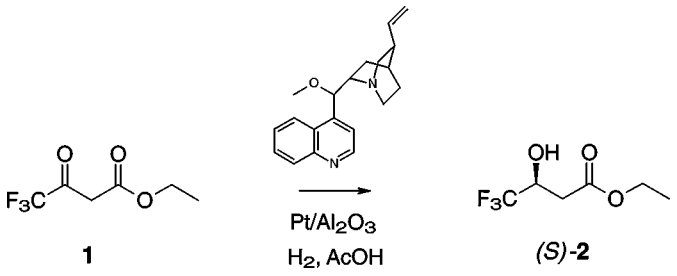


SCHEME 1. Hydrogenation of ethyl-4,4,4-trifluoroacetoacetate **1** over chiraly modified Pt.

EXPERIMENTAL

Ethyl-4,4,4-trifluoroacetoacetate **1** (Fluka, purum) and ethyl pyruvate (Fluka, purum) were distilled before use and the solvents were dried over Na. O-methyl cinchonidine (MeOCD) was synthesized as described before (35). The 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was prereduced in flowing hydrogen for 90 min at 400°C. After being cooled to room temperature in hydrogen, the catalyst was transferred to the reactor without exposure to air.

Hydrogenations were carried out at room temperature 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 a computerized constant volume constant pressure equipment (Büchi BPC 9901). According to the *general procedure* 110 ± 3 mg catalyst was added to a mixture of 5.5 mg (18 μmol) MeOCD and 0.34 g (1.85 mmol) reactant in 5 ml solvent ($c = 0.37$ mol/l). When the reaction mixture was preequilibrated (in the presence of the modifier) for 15 h before the reaction, the catalyst was added approximately 5 min before initiating hydrogenation. The autoclave was opened for a short period of time in order to collect samples (ca. 2–2.5 min delay for each sampling). These periods were taken into account for the calculation of reaction time.

Yields and enantioselectivities were determined by direct gas chromatographic analysis of the reaction mixture, using a Chirasil-DEX CB (Chrompack) capillary column in an HP 6890 gas chromatograph. Enantioselectivity is expressed as ee $(\%) = 100 \times |(R - S)|/(R + S)$. The actual or incremental ee is calculated as $\Delta ee = (ee_1 Y_1 - ee_2 Y_2)/(Y_2 - Y_1)$, where Y represents the yield to the α,α,α-trifluoro-β-hydroxyester (**2**), and index 2 refers to a sample taken subsequent to sample 1.

NMR spectra were recorded on Bruker DPX 200 and DPX 300 spectrometers. Sample concentration mimicked the conditions in the general reaction procedure (0.37 mol/l). Keto and enol forms, hydrate and hemiketals were identified by ^1H, ^{13}C, and ^{19}F NMR-spectroscopy (36). Relative amounts of the different compounds were calculated by integration of the peak areas in the ^{19}F spectra.

RESULTS

Catalytic Experiments

Studying the hydrogenation of **1** in alcoholic solvents we found striking deviations in enantioselectivites and reaction rates, depending on the chemical structure of alcohol. For example, the reaction in 2-propanol was fast and selective, affording up to 70% ee to the (*S*)-enantiomer. In ethanol, the reaction was at least an order of magnitude slower and the ee was around 20%.

Searching for an explanation, we investigated the influence of preequilibration of the reaction mixture before hydrogenation as illustrated in Figs. 1 and 2. In 2-propanol without preequilibration the ee remained almost constant up to 70% yield to **2**. When the reaction mixture (without Pt/alumina) was equilibrated for 15 h before hydrogenation, both the initial rate and ee were considerably lower in the whole conversion range. Interestingly, calculation of the incremental or actual ee indicated close to racemic product formation in the final period of both reactions, independent of preequilibration. The effect of preequilibration in ethanol was considerably smaller than in 2-propanol. Though preequilibration diminished the ee in the whole conversion range, the two reactions afforded almost the

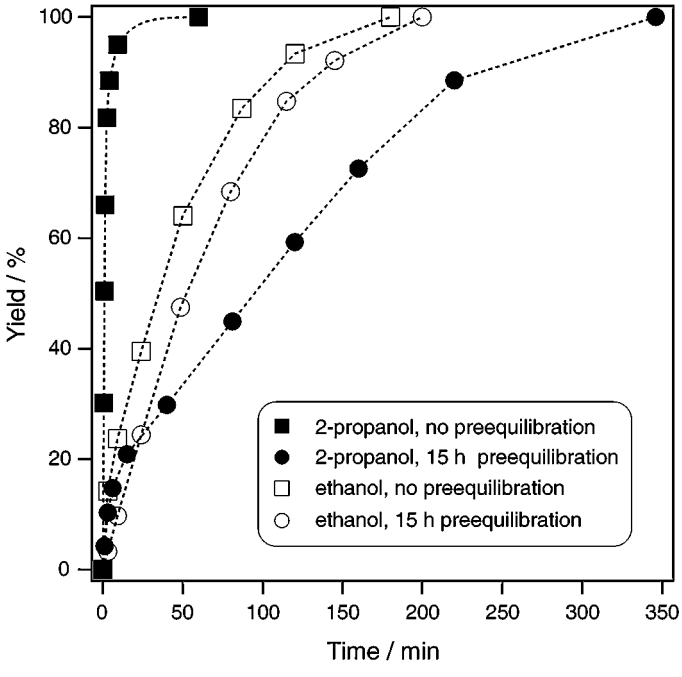


FIG. 1. Kinetic curves of the hydrogenation of **1** in ethanol and 2-propanol, with and without preequilibration. Reaction conditions according to general hydrogenation procedure.

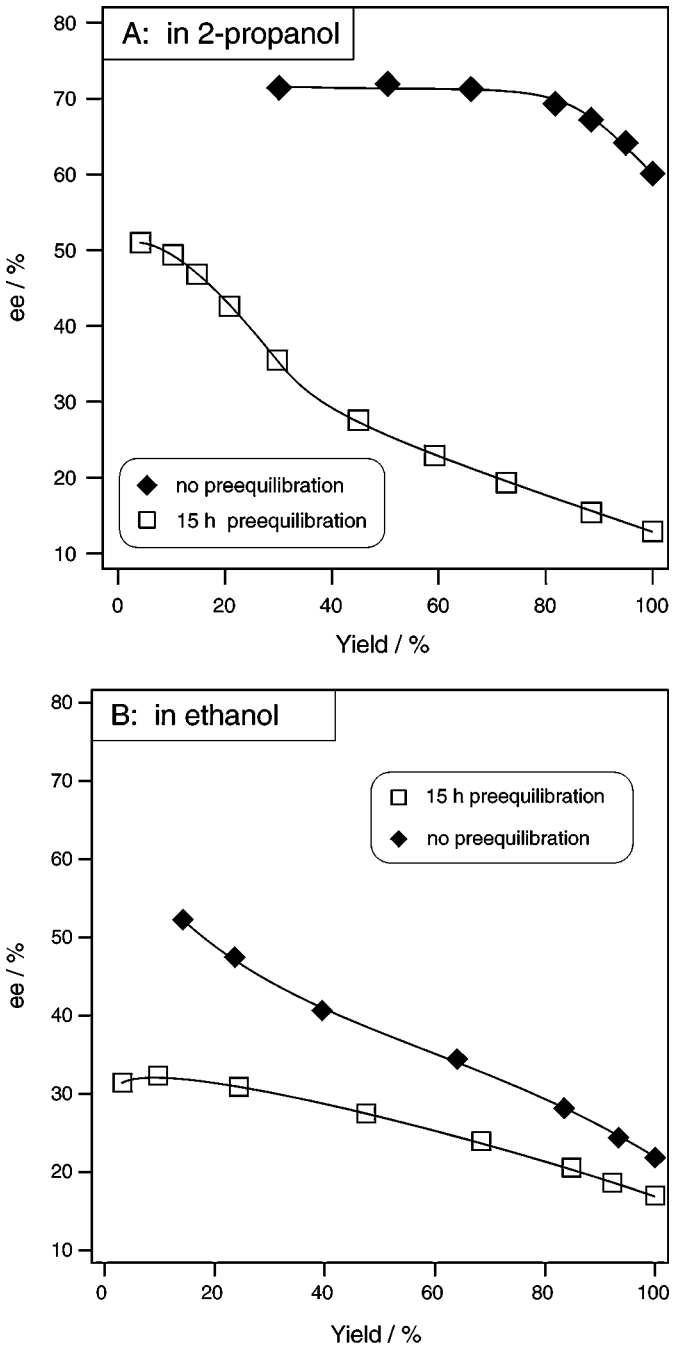


FIG. 2. Change of ee with increasing yield to **2**, with and without preequilibration. (A) Hydrogenation in 2-propanol; (B) hydrogenation in ethanol. Reaction conditions are according to general hydrogenation procedure.

same (integral) ee at full conversion (Fig. 2B). Considering the reaction rates, the small difference originates from the initial period, up to about 20% yield (Fig. 1).

We must mention that the minor decay in ee at the end of the hydrogenation reaction in 2-propanol (Fig. 2A) is not a general feature of the reaction without preequilibration. Under partly different conditions (other Pt/**1** and MeOCD/**1** ratios, constant MeOCD/Pt ratio) the ee did not change significantly and 70% ee was achieved at full conversion. An example is shown in Table 1 (first entry).

A possible explanation for the drop of ee with yield in alcoholic solvents could be the destruction of the chiral modifier during reaction. Hydrogenation of the terminal C═C bond has no significant influence, but saturation of one or both aromatic rings of the cinchona alkaloid has been shown to result in a partial or complete loss of enantio-differentiation in the hydrogenation of ethyl pyruvate (37–39). On the basis of the correlation between modifier concentration and ee in the hydrogenation of **1** we estimate that under standard conditions more than 90% of the initial amount of MeOCD must be destroyed in order to observe a considerable, higher than 10% drop in ee. To clarify the role of modifier consumption we repeated the experiment in Table 1 (entry 1), but first the reaction mixture was stirred in hydrogen for 4 h in the absence of **1**. Afterward, **1** was added and hydrogenated. The reaction afforded 68% ee, and even the average rate of hydrogen consumption was similar to that of the reference reaction. Obviously, the unusual variations of ee presented in Fig. 2 cannot be attributed to the partial destruction of MeOCD.

Another possible explanation for the lower ee and rate obtained after preequilibration is that during equilibration—in the absence of Pt/alumina but in the presence of MeOCD as a base catalyst—some side reactions occurred. The byproducts could adsorb on Pt and diminish the rate and selectivity of the hydrogenation of **1**. We have shown recently (40) that CD as a base can efficiently catalyze the aldol reaction of ethyl pyruvate. However, this reaction was not detectable even after several hours when MeOCD and **1** interacted in an alcoholic solvent. According to GC and NMR analysis, equilibration of **1** resulted in no other products besides the equilibrated species, which will be discussed in the next chapter.

NMR Spectroscopic Study of Hemiketal Formation

The differences presented in Figs. 1 and 2 cannot be explained by a general solvent effect as both 2-propanol

TABLE 1

Effect of Prehydrogenation of the Modifier on the Enantioselective Hydrogenation of Ethyl-4,4,4-trifluoroacetoacetate (1) in 2-propanol

Conditions	Final ee [%]	Time for 50% conversion [min]
Usual procedure	70	9
Hydrogenation of **1** after prehydrogenation of MeOCD for 4 h	68	10

Note. Forty-two milligram catalyst, 2 mg MeOCD, 5 ml solvent, 0.34 g reactant, 10 bar, room temperature.

and ethanol are protic polar solvents. Their polarity characterized by the empirical solvent parameter E_T^N (0.546 and 0.654, respectively) or relative permittivity ε (19.9 and 24.6, respectively) are similar (41). The most feasible explanation for the remarkable influence of solvent structure is the hemiketal formation from **1** and the alcoholic solvent, and the subsequent hydrogenolysis to **2**, the reaction route of which may compete with the direct hydrogenation of the keto form of **1**. Hemiketal formation does not require the presence of a metal hydrogenation catalyst or hydrogen, which is shown by the striking influence of preequilibration. During preequilibration only the modifier is present which acts as a base catalyst (pK_a of quinuclidine: 10.9 (42)).

The species formed during equilibration of **1** with the alcoholic solvents were identified by NMR. The spectra are rather complex, because **1** exists as a mixture of the keto (**1a)** and enol forms (**1b)** (Scheme 2). Furthermore, even the trace amounts of water present in the commercial deuterated alcohols lead to the formation of hydrate **3** (29). Despite this complex equilibrium, it was possible to identify the hemiketals **4** and **5** by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy as the most abundant species present in ethanol and 2-propanol, respectively.

The kinetics of equilibration were investigated by ^{19}F-NMR spectroscopy. In these spectra every species gave a single sharp peak which could accurately be integrated. In ethanol, the equilibration was very fast at the beginning and the keto and enol forms (**1a** and **1b)** reached their low equilibrium concentrations within 20 min (Fig. 3). In a second stage of equilibration, the amount of **3** decreased in favor of the hemiketal **4** while the concentrations of **1a** and **1b** remained constant. Equilibrium concentrations shown in Table 2 were reached after approximately 9 h. A similar picture was observed in deuterated 2-propanol, except that equilibration was remarkably slower. In this solvent, the hydrate formation was partially suppressed by drying the solvent over molecular sieve before use. Seventy-five percent hemiketal **5** formed in 65 h, a value which still does not yet represent the equilibrium concentration. Another important feature of equilibration in the secondary alcohol was that the amount of keto form did not drop below 1% (Table 2). Thus, the hemiketal/keto ratio is much lower in 2-propanol than in ethanol. These ratios, comparing the concentrations of the two most likely reacting species, are shown in Fig. 4 as a function of equilibration time. In 2-propanol the highest measured value of **5/1a** was 65 after 65 h. For comparison, achieving the same hemiketal/keto ratio in ethanol **(4/1a)** required only 17 min, and the highest value in this solvent measured after 13 h was 495.

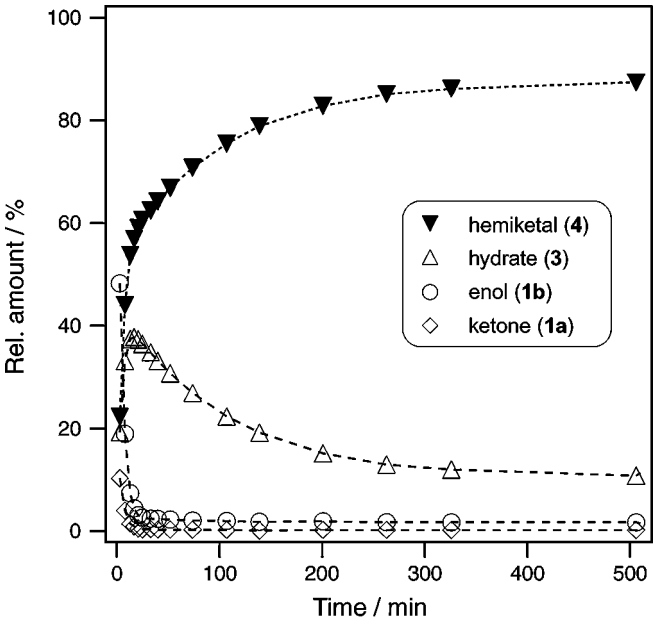


FIG. 3. Equilibration of **1** in ethanol measured by ^{19}F NMR-spectroscopy. Initial concentrations are set according to the genal hydrogenation procedure (i.e., in the presence of MeOCD).

An alternative explanation for the observed changes in the conversion-dependence of ee might be the hemiketal formation of **1** with the (chiral) secondary alcohol product **2**. However, no hemiketal or other product could be observed by NMR even in concentrated mixtures of **1** and **2**, with a detection limit of 1%. The extent of hemiketal formation in ethanol and 2-propanol, and the absence of this

TABLE 2

Equilibrium Compositions in Ethanol and 2-Propanol, Concentrations According to General Hydrogenation Procedure

Compound	Solvent	Ketone [%]	Enol [%]	Hydrate [%]	Hemiketal [%]	Hemiketal/ Ketone
1	ethanol	0.17	1.2	12.1	86.6	495
1[a]	2-propanol	1.1	7.2	20.3	71.4	65
Ethyl pyruvate	ethanol	33.1	—	—	66.9	2.02
Ethyl pyruvate[b]	ethanol	26	—	—	74	2.85

[a] Measured after 65 h (equilibration not yet complete).
[b] Diluted solution (0.035 mol/l instead of 0.37 mol/l).

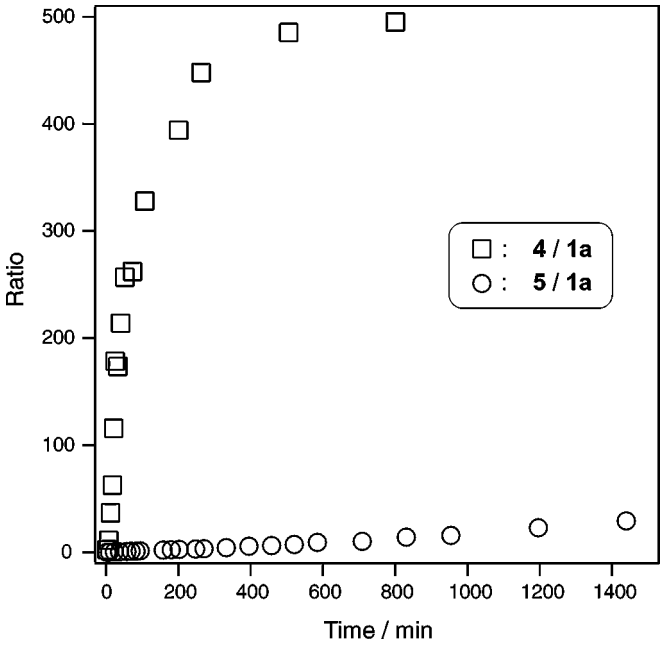


FIG. 4. Comparison of the hemiketal/keto ratios in ethanol (**4/1a**) and 2-propanol (**5/1a**) during equilibration, as followed by ^{19}F NMR-spectroscopy. Initial concentrations are set according to the general hydrogenation procedure (i.e., in the presence of MeOCD).

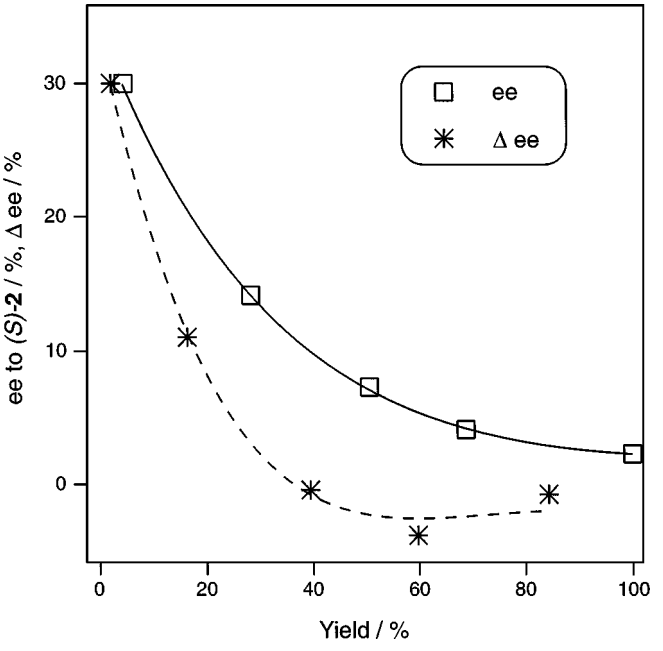


FIG. 5. Variation of ee and incremental ee (Δee) with yield to **2** in methanol. Reaction conditions are according to general hydrogenation procedure; 1.85 mmol of the isolated hemiketal in 5 ml methanol.

transformation with **2**, is in agreement with the expectation that the equilibrium constant of the reaction is increased by electron withdrawing (activating) substituents in α-position to the carbonyl group. The opposite effect is expected for electron-attracting substituents in the alcohol, and in general any substituent in α-position to the OH group (steric hindrance) (43).

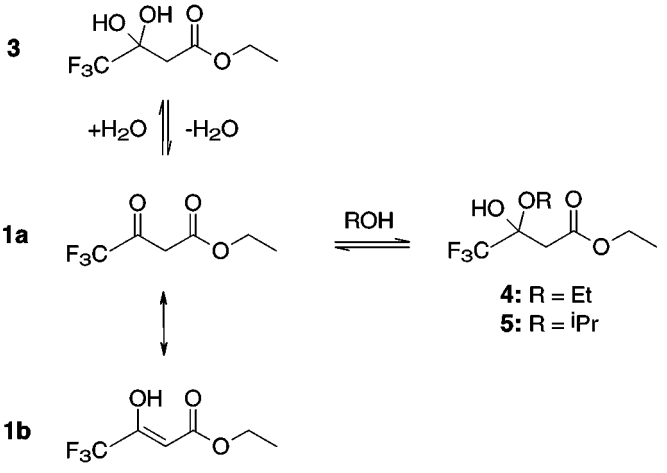
Isolation of the Hemiketal and Its Hydrogenolysis in Methanol

To confirm the feasibility of hemiketal hydrogenolysis on Pt/alumina, we have synthesized the hemiketal of **1** in methanol, which is a fast reaction even without a catalyst. After removal of methanol the product containing dominantly the hemiketal (with small amounts of **1a**, **1b**, and **3)** could be isolated. It was stable in nonalcoholic solutions (no reequilibration was observed) for several days. Hydrogenolysis of this hemiketal in methanol with the MeOCD-Pt/alumina system resulted in a rapid decrease of ee with conversion or yield (Fig. 5). The actual or incremental ee (Δee) dropped to around zero at a yield of about 30% and remained in this range until full conversion. In this reaction period hemiketal hydrogenolysis seems to be exclusive. This result strongly supports our suggestion that hydrogenolysis of the hemiketal is responsible for the observed decrease in ee during hydrogenation of **1** in alcoholic solvents.

DISCUSSION

Reactivity of Various Species during Hydrogenation

We propose that the unusual solvent effect uncovered during hydrogenation of **1** in simple aliphatic primary and secondary alcohols can be explained by the competing hydrogenation of the keto carbonyl group of **1a** and hydrogenolysis of the hemiketal formed with excess alcohol according to Scheme 2. Hemiketal formation with an



SCHEME 2. Equilibration of ethyl-4,4,4-trifluoroacetoacetate **1** in ethanol and 2-propanol as solvents in the presence of trace amounts of water.

activated carbonyl group is a facile reaction and any base or acid catalyzes it. With short chain primary aliphatic alcohols (MeOH, EtOH) the reaction runs smoothly even in the absence of a catalyst.

In 2-propanol, hydrogenation of the keto form **1a** is the prevailing, fast reaction at the beginning of the reaction. During reaction, the hemiketal/keto ratio (**5/1a**, Scheme 2) slowly enhances due to consumption of the keto form and to the increased time available for equilibration (Fig. 4). Additionally, hydrogenolysis of the C–O bond is slow compared to C═O hydrogenation (31), thus transformation of the hemiketal **5** becomes significant only at high conversion, when the **5/1a** ratio is relatively high. The drop in the integral ee above 80% yield to **2** (Fig. 2) indicates this shift in the reaction pathway. The gradual change in the reaction mechanism is confirmed by the close to zero actual (or incremental) ee in the final period of the reaction. When equilibration precedes the hydrogenation reaction, the influence of hemiketal hydrogenolysis is significant already at low conversion as indicated by the considerably lower rate and ee (Figs. 1 and 2A).

In the primary alcoholic solvent, ethanol hemiketal formation is fast and the hemiketal/keto ratio **(4/1a)** reaches a very high level within a short period of time (Figs. 3 and 4). Accordingly, hemiketal hydrogenolysis to form **2** is significant from the beginning of the hydrogenation process, even without preequilibration. It is also obvious that the effect of preequilibration on the reaction rates (Fig. 1) and enantioselectivities (Fig. 2B) are small in this solvent.

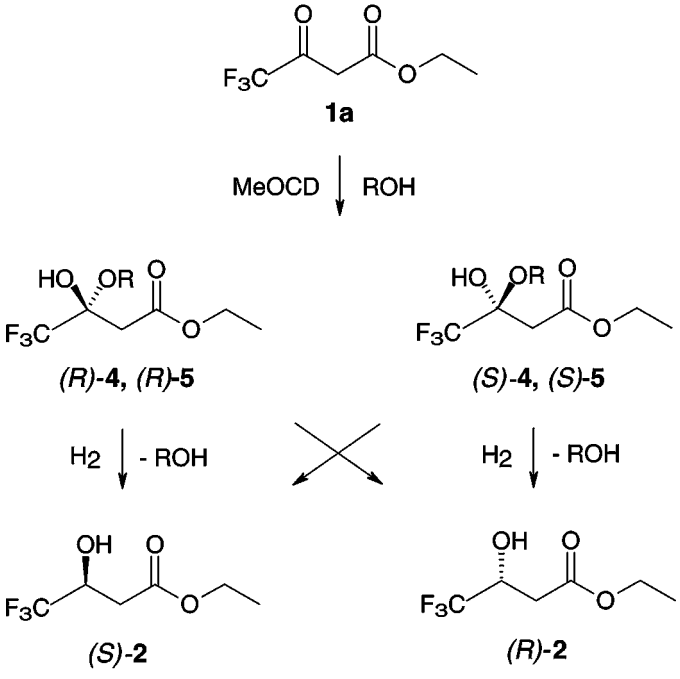
The relative contribution of hemiketal hydrogenolysis to the product distribution depends on the actual hemiketal/keto ratio and the relative reactivities of these species. NMR analysis revealed that in the time scale of the hydrogenation reactions (50–350 min) the hemiketal/keto ratio is two orders of magnitude higher in ethanol than in 2-propanol (Fig. 4). Figure 1 shows that the kinetic curves in ethanol lie between those obtained in 2-propanol. It follows that hydrogenolysis of **4** (in ethanol) is faster than the corresponding hydrogenolysis of **5** (in 2-propanol). The slower formation and hydrogenolysis of hemiketal in the secondary alcohol is attributed to steric effects (43).

As shown in Scheme 2, in alcoholic solvents the keto form **1a** equilibrates to hemiketals **4** or **5**, but there are always certain amounts of enol **1b** and hydrate **3** present in the complex equilibrium. It is very unlikely that direct hydrogenolysis of **3** would significantly contribute to the product formation. The rate of formation of **3** with the water residue present in the reaction mixture is the same in both solvents. The amount of **3** is expected to be very similar in all experiments, because the same drying procedures were applied for all reaction components, including the catalyst pretreatment in flowing hydrogen at 400°C. Furthermore, we have shown recently that hydrogenolysis of **3** is orders of magnitude slower than hydrogenation of **1a** (29).

NMR analysis revealed that the keto/enol ratio was always constant, independent of the stage of equilibration (Fig. 3). Even in the initial phase of equilibration in ethanol, which is a fast process, the keto/enol ratio did not change. This is an indication that the keto–enol interconversion is faster than all other equilibration reactions and, more importantly, faster than any hydrogenation reaction revealing a decrease in ee with conversion (Fig. 1). This implies that the keto/enol ratio remained constant during reactions and the effects observed in the time scale of several minutes to several hours cannot be attributed to a shift from hydrogenation of the keto to the enol form. This conclusion is in agreement with an earlier suggestion that the enol form of another activated ketone, ethyl pyruvate, is not reactive over cinchona-modified Pt (26). Hence, we conclude that **1b** and **3** are spectator species in the hydrogenation of **1** in alcoholic solvents even though they influence the outcome of the reaction by affecting the hemiketal/keto ratios (Table 2).

Stereochemical Aspects of Hemiketal Formation

The explanation for the drop in ee with increasing proportion of hemiketal hydrogenolysis requires a closer inspection of this reaction pathway (Scheme 3). The base-catalyzed (MeOCD) formation of hemiketal **4** or **5** creates a stereogenic center and the chiral molecule is



SCHEME 3. Stereochemical aspects of the formation of hemiketals **4** and **5** and their subsequent hydrogenolysis to **2**.

hydrogenolyzed in the subsequent reaction step. The first step can provide a racemic mixture of the two enantiomeric hemiketals, or it may be an enantioselective reaction when the modifier acts as a chiral N-base catalyst. We have followed the hemiketal formation in ethanol with GC analysis and optical rotation measurements and found that the hemiketal was racemic. In the second reaction step (Scheme 3), which takes place on the Pt surface, the C atom remains the stereogenic center but the OR group is replaced by H. It is not yet clear whether the modifier interacts with the hemiketal during hydrogenolysis or not. As the Δee values measured at high conversions, where hemiketal hydrogenolysis is the dominant reaction pathway, are close to zero (Fig. 5) the stereoselectivity in the second reaction step seems to be negligible.

Role of Hemiketal Formation in the Hydrogenation of Other Activated Ketones

In the hydrogenation of ethyl pyruvate, which is the most studied reaction over cinchona modified Pt, hemiketal formation and its kinetics have already been described in (30). Under the conditions applied, no evidence could be found for a significant extent of hemiketal hydrogenolysis to ethyl lactate, even though the hemiketal formation was fast in the presence of cinchonidine. Comparing the hydrogenation of ethyl pyruvate and **1**, there may be two major reasons for this deviation. As discussed above, the hemiketal/keto ratio and the reactivities of these species determine the relative contribution of the two reaction pathways. Unfortunately, the relative reactivities of the keto and hemiketal species in the two reactions cannot reliably be estimated. But in the case of **1** the hemiketal/keto ratio is bigger by more than two orders of magnitude (ethanol) than that measured for ethyl pyruvate (Table 2). This huge difference is partly due to enolization and hydrate formation from **1**, in which the equilibrium reactions are negligible with ethyl pyruvate. The high degree of enolization is well known for fluorinated β-ketoesters and is attributed to extra stabilization via hydrogen bonding between the enolic OH and F groups (44). A similar argument may account for the high stability of the hemiketal and the hydrate of **1**.

We have reinvestigated the hydrogenation of ethyl pyruvate and studied the influence of some reaction parameters which can influence the hemiketal/keto ratio. The reaction under standard conditions afforded constant ee up to full conversion. In order to increase the hemiketal/keto ratio, the hydrogenation was performed in a more diluted ethanolic solution (Table 2), and the hydrogen pressure was decreased to 1 bar to slow down the whole hydrogenation process. The biggest effect detected was a decrease in ee from 64% at medium conversion to 61% at full conversion. Though this shift is small, it is significant (reproducibility of GC analysis $\pm$0.2%), and the change is in agreement with the observations in the hydrogenation of **1**. This is an indication that hemiketal hydrogenolysis may play a role in the hydrogenation of ethyl pyruvate in alcoholic solvents, especially at high conversions, where the hemiketal/keto ratio reaches a relatively high level. Hemiketal formation must be accounted for when interpreting the decrease in ee with higher conversion. Together with the slow consumption of cinchonidine during reaction (37–39), it can explain the loss in enantioselectivity observed at the end of the reaction.

CONCLUSIONS

Comparative enantioselective hydrogenation of ethyl 4,4,4-trifluoroacetoacetate **1** in primary and secondary alcohols and the effect of preequilibration in the presence of the cinchona derivative MeOCD, demonstrate that formation and hydrogenolysis of the hemiketal is a feasible reaction pathway. This reaction pathway can efficiently compete with the direct hydrogenation of the keto form on Pt only when the reaction conditions favor the development of high hemiketal/keto ratios and the reactivity of hemiketal is sufficiently high. These conditions are fulfilled in primary alcoholic solvents. The formation of racemic hemiketal during preequilibration, and the close to zero incremental or actual ee obtained in hydrogenations after preequilibration in alcohol, indicate that the whole reaction pathway via the hemiketal is not stereoselective.

The reaction pathway via the hemiketal may be important in the hydrogenation of other activated ketones over cinchona-modified Pt. The hemiketal/keto ratio strongly depends on the nature of activating group in α-position to the keto-carbonyl group. The outstanding effect of alcoholic solvents on the hydrogenation of **1** is likely due to extra stabilization via H-bonding between the F and OH groups of hemiketal, enol, and hydrate species. A useful conclusion from these observations is that due care is necessary when basic kinetic or mechanistic studies aimed at understanding the enantioselective hydrogenation of activated ketones are carried out in alcoholic solvents.

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