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RESEARCH NOTE

# First Enantioselective Hydrogenation of a Trifluoro-$\beta$-ketoester with Cinchona-Modified Platinum

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**A series of trifluoromethyl ketones possessing different functional groups were hydrogenated over $Pt/Al_2O_3$ modified by cinchonidine and *O*-methylcinchonidine. The highest enantiomeric epcess of 90% was achieved in the hydrogenation of ethyl 4,4,4-trifluoroacetoacetate. The remarkable variation of enantioselectivity in the synthesis of various $\alpha,\alpha,\alpha$-trifluoromethyl alcohols is interpreted by electronic and steric effects. Future mechanistic studies have to clarify the unexpectedly big influence of acidic solvent and the special role of the (C9)–OH group in cinchonidine.**


*Key Words:* **enantioselective hydrogenation; cinchonidine; platinum–alumina; trifluoromethyl ketones.**

## 1. INTRODUCTION

Chiral-fluorinated compounds have a great potential as antiinflammatory and cardiovascular drugs or anticancer and antiviral agents (1). A possible synthetic route to $\alpha,\alpha,\alpha$-trifluoromethyl alcohols is the asymmetric hydrogenation of trifluoromethyl ketones. Various chiral boranes and aluminium hydride reagents provided very good results in the hydrogenation of aromatic and nonaromatic trifluoromethyl ketones. The chemical yields are generally above 80% and the enantiomeric excess (ee's) are 90% or higher under very mild conditions (2, 3). Enzymatic reduction by the use of bakers' yeast or *Geotrichum candidum* acetone powder afforded moderate to almost perfect enantioselectivities (4, 5). Homogeneous chiral transition metal catalysts, which perform excellently in the enantioselective hydrogenation of a variety of ketones (6), have been used only for the hydrogenation of 2,2,2-trifluoroacetophenone and some of its aryl-substituted derivatives, affording up to 96% ee at 100% conversion (7, 8).

We have reported for the first time (9, 10) that 2,2,2-trifluoroacetophenone can be hydrogenated with around 60% ee over $Pt/Al_2O_3$ modified with cinchonidine (CD). But recently the hydrogenation of benzyltrifluoromethyl ketone afforded rather poor enantioselectivity, only 18% (11). To clarify whether the Pt–cinchona system is a generally useful catalyst for the synthesis of $\alpha,\alpha,\alpha$-trifluoromethyl alcohols, we have extended our investigations to a broader range of substrates, using CD and some of its simple derivatives as chiral modifiers for Pt. These studies provide further insight into the crucial role of electronic and steric effects in the asymmetric hydrogenation of activated ketones on chirally modified Pt.

## 2. METHODS

All substrates, CD and CD hydrochloride (CD · HCl), were used as received (Fluka, Aldrich). *O*-Methylcinchonidine (MeOCD) was synthesized as described before (12). A 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. Platinum dispersion after heat treatment was 0.27, as determined by TEM.

Hydrogenations were carried out in a magnetically stirred 100-ml stainless steel autoclave equipped with a 50-ml glass liner and a PTFE cover. Under standard conditions $42 \pm 2$ mg of catalyst, 1.84 mmol of substrate, 6.8 $\mu$mol of modifier, and 5 ml of solvent were stirred magnetically (1000 rpm) under a constant hydrogen pressure of 10 bar. The reaction was followed by monitoring of the hydrogen uptake (Büchi BPC 9901). The experiments were carried out at room temperature except for the volatile compound **7**.

The products were isolated and identified by NMR spectroscopy. The ee was determined by direct gas chromatographic analysis of the reaction mixture, using a HP 6890 gas chromatograph and a Chirasil-DEX CB (Chrompack) capillary column. In the case of **7** the product was derivatized with acetic acid anhydride and

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4-dimethylaminopyridine. The enantiomeric excess is expressed as ee(%) = 100 × |(*R*−*S*)|/(*R* + *S*).

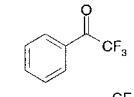
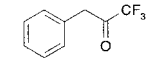
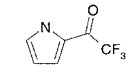
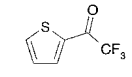
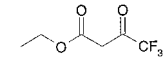
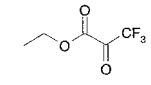
## 3. RESULTS

The potential of the Pt–cinchonidine system in the enantioselective hydrogenation of trifluoromethyl ketones is illustrated in Table 1. A broad range of substrates have been selected, compounds which possess alkyl, alkyaromatic, aromatic, heteroaromatic, or ester functions. Although the hydrogenation of **1** and **2** has already been reported, these substrates are also included here to show the influence of structural variations in the modifier. Most of the experiments were carried out in toluene and acetic acid, solvents which give generally the best results in the hydrogenation of activated ketones over the Pt–CD system (13, 14). The only exception is the hydrogenation of **1**, a reaction in which not toluene but dichlorobenzene is the best solvent.

Variation of the structure of trifluoromethyl ketones resulted in strikingly different reaction rates and enantioselectivities (Table 1). In general, hydrogenations in the presence of cinchona alkaloid were faster than the corresponding reactions over the unmodified catalyst. On the basis of the reaction time necessary to achieve 50% conversion, the highest rate acceleration (by a factor of 5.5) was measured

**TABLE 1**

**Enantioselective Hydrogenation of Substituted Trifluoromethyl Ketones under Standard Conditions**

| N° | Substrate | | Toluene + CD | Toluene + CD · HCl | Acetic acid + CD |
|---|---|---|---|---|---|
| 1 |  | ee (%) | 62[a] | 70[a] | 6 |
| | | conv. (%) | 100 | 100 | 43 |
| | | time (h) | 1.5 | 1.5 | 1.5 |
| 2 |  | ee (%) | 10 | 18 | 5 |
| | | conv. (%) | 98 | 83 | 100 |
| | | time (h) | 3 | 2 | 2 |
| 3 |  | ee (%) | 56 | 60 | 30 |
| | | conv. (%) | 93 | 81 | 43 |
| | | time (h) | 2 | 3.5 | 3 |
| 4 |  | ee (%) | 3[b] | 2[b] | 0[b] |
| | | conv. (%) | 6 | 7 | 14 |
| | | time (h) | 3 | 3 | 3 |
| 5 |  | ee (%) | 49 | 42 | 70 |
| | | conv. (%) | 100 | 100 | 100 |
| | | time (h) | 1 | 1 | 1.5 |
| 6 |  | ee (%) | 5 | — | — |
| | | conv. (%) | 40 | — | — |
| | | time (h) | 3 | — | — |
| 7 |  | ee (%) | 18[c] | 18[c] | 6 |
| | | conv. (%) | 100 | 100 | 70 |
| | | time (h) | 1 | 1.5 | 4 |

[a] Solvent: 1,2-dichlorobenzene, 3.6 mmol of substrate, 2 bar hydrogen pressure.

[b] 50 bar hydrogen pressure.

[c] Reaction at 0°C.

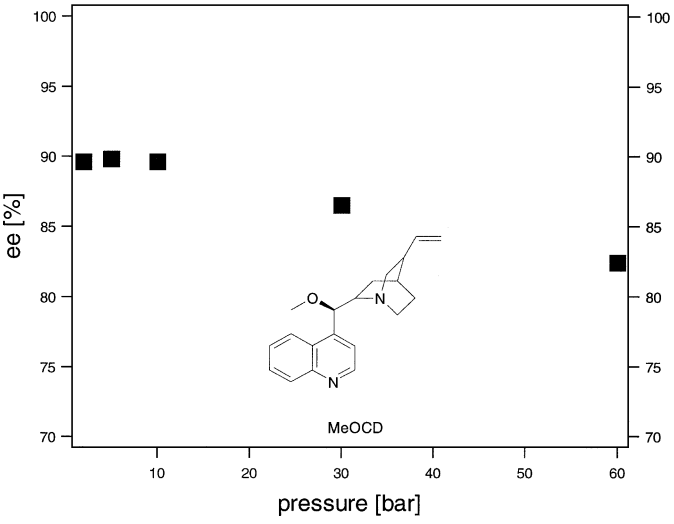



**FIG. 1.** Pressure dependence of the hydrogenation of **5** under standard conditions in acetic acid, using MeOCD as the modifier.

in the reduction of **7**. The reaction times in toluene, with or without CD as the modifier, were 20 and 110 min, respectively. Though many reactions were easy and the hydrogen consumption ceased within 1–1.5 h, the thiophene ring in **4** strongly poisoned the catalyst and high conversion could not be achieved, even after prolonged reaction time and at higher hydrogen pressure. A comparison of the results obtained with **3** and **4** clearly demonstrates the detrimental effect of the sulphur heteroatom.

Although in the experiments shown in Table 1 only two solvents and two chiral modifiers were tested, 60–70% ee was achieved in the hydrogenation of the substrates **3** and **5**. Optimization of reaction conditions and modifier structure has not yet been attempted, but in two cases some more reaction parameters were varied. In the hydrogenation of **1** the surface hydrogen concentration on Pt was reduced by increasing the amount of catalyst (i.e., operating the reactor in the mass transport limited region), which resulted in a small increase in ee from 70 to 74% in dichlorobenzene. This value represents the highest ee achieved in this reaction with a solid catalyst (9–11). In the hydrogenation of **5**, replacing CD by MeOCD enhanced the ee from 70% to 90% in acetic acid. Further improvement by varying the pressure or the amount of modifier failed, as illustrated in Figs. 1 and 2. These additional experiments, together with the results in Table 1, indicate that cinchona-modified Pt is an efficient catalyst for the synthesis of trifluoromethyl alcohols, albeit the best conditions vary for each substrate and optimization may require considerable further effort.

## 4. DISCUSSION

It was proposed earlier (15) that the enantioselective hydrogenation over cinchona-modified Pt is limited to *trans*-$\alpha$-dicarbonyl compounds such as $\alpha$-ketoesters or

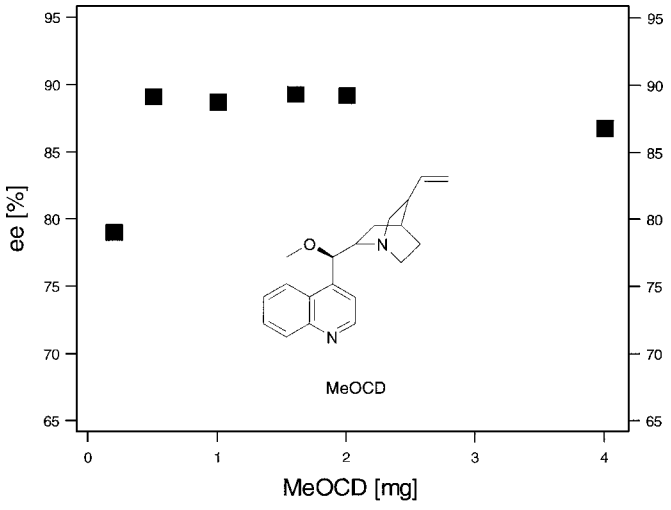



**FIG. 2.** Influence of the amount of modifier MeOCD on the enantiomeric excess in the hydrogenation of **5** under standard conditions in acetic acid.

$\alpha$-diketones. The successful hydrogenation of **1** (9, 10) and ketopantolactone (16) was the first piece of evidence against this postulate, indicating that the real requirement for the substrate is the presence of an electron-withdrawing group in the $\alpha$ position. The recent highly enantioselective hydrogenation of $\alpha$-ketoacetals (17, 18) provides additional evidence in this direction.

The results in Table 1 allow further refinement concerning the role of an electron-withdrawing group in the substrate. Ethyl trifluoropyruvate **6** possesses two strong electron-withdrawing groups on both sides of the carbonyl group. Nevertheless, hydrogenation of this compound afforded very poor results. Hydrogen uptake ceased at moderate conversion and the ee was very low. A possible reason for this unexpected behavior is that the highly activated carbonyl compound reacts with the modifier, as evidenced by NMR spectroscopy. The $^{1}$H-NMR and $^{13}$C-NMR spectra of the mixture of **6** and CD could not be interpreted due to overlapping of the signals, but the $^{19}$F signal of **6** at $-76$ ppm disappeared in favor of a new main peak at $-81.5$ ppm. When 2-propanol was used to mimick the secondary OH function of CD, the rapid and complete conversion of **6** to the corresponding hemiketal was confirmed by $^{1}$H-, $^{13}$C- and $^{19}$F-NMR (with a $-76$- to $-82$-ppm shift in the latter case). Apparently, the hemiketal of **6** and CD is a poor modifier in the enantioselective hydrogenation of **6**.

In case of 1,1,1-trifluoroacetone (**7**) the steric difference between the $CH_3$ and the $CF_3$ group is very small, which can explain why the enantio-differentiation is so moderate in this reaction. The structure of 3-phenyl-1,1,1-trifluoropropan-2-one (**2**) is very similar to that of **1**. The only difference is an additional methylene group between the carbonyl group and the aromatic ring in **2**, which resulted in a strong negative effect on the ee. It is assumed that the more flexible, nonplanar structure of **2** influences both the adsorption on the Pt surface and the interaction with the modifier. These examples demonstrate that steric as well as electronic effects determine the enantio-differentiation over the Pt–cinchona system.

The examples in Table 1 provide some information concerning the substrate–modifier interaction during the enantio-differentiating step. On the basis of the effect of replacing toluene by acetic acid, the substrates may be divided into two groups. In acetic acid the ee dropped dramatically in all reactions except in the hydrogenation of **5**, where the ee increased by 21%. It is not clear yet what is the role of protonation of the quinuclidine N atom by acetic acid in the substrate–modifier interactions. Another intriguing observation is the unexpectedly high ee obtained by replacing CD with MeOCD in the hydrogenation of **5**. For comparison, in the hydrogenation of $\alpha$-ketoesters with the same catalyst the difference between the ee's obtained in toluene or acetic acid, and with CD or MeOCD, was only 2–3% (14). Besides, *ab initio* calculations indicated that the conformations of CD and MeOCD are similar (dominance of "open 3" conformation (19)). It was proposed earlier (9, 10, 13) that in the enantio-differentiating step the quinuclidine N atom of CD interacts with the O atom of the keto carbonyl group of the substrate via a H bond (N–H–O-type interaction), and the OH group of CD is not involved in this interaction. The significant positive effect of replacing the hydroxy group of CD by a methoxy group can be explained by the importance of another type of substrate–modifier interaction via the OH group which is competitive enough to diminish the ee.

## 5. CONCLUSIONS

The enantioselective hydrogenation of various trifluoromethyl ketones shown in this work demonstrates the potential of cinchona-modified Pt for the synthesis of chiral-fluorinated alcohols. Additional functional groups, such as an ester function in the $\beta$ position or amines, are not detrimental to enantio-differentiation. Hydrogenation of trifluoromethyl ketones represents a new example where up to 90% ee can easily be achieved with a chirally modified metal hydrogenation catalyst. The poor ee's obtained with 3-phenyl-1,1,1-trifluoropropan-2-one (**2**) and 1,1,1-trifluoroacetone (**7**) provide useful hints concerning the importance of both electronic and steric effects in the enantio-differentiating step. These observations, together with the unexpectedly high effects of an acidic solvent and the protection of the OH group of CD, are good starting points for future mechanistic studies.

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