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Platinum-catalyzed enantioselective hydrogenation of aryl-substituted trifluoroacetophenones

Matthias von Arx, Tamas Mallat and Alfons Baiker*

Laboratory of Technical Chemistry, Swiss Federal Institute of Technology, ETH-Hönggerberg HCI, CH-8093 Zürich, Switzerland

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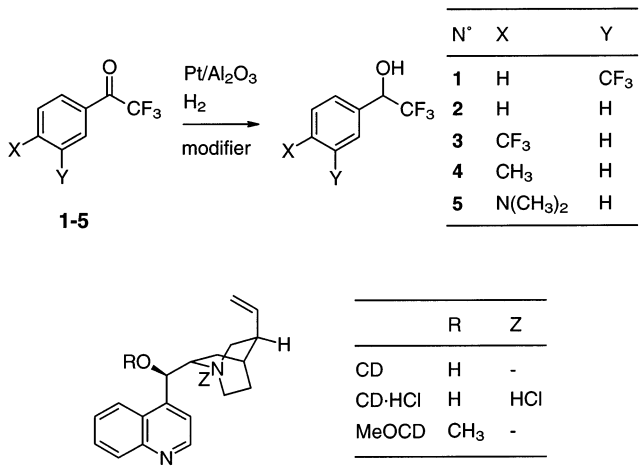
Abstract—The hydrogenation of 2,2,2-trifluoroacetophenones with different aryl-substituents (CF_3, $N(Me)_2$ and Me) has been studied over Pt/Al_2O_3 modified by cinchonidine, its hydrochloride or *O*-methyl cinchonidine. Electron-withdrawing groups increased and electron-releasing groups decreased the rate and enantioselectivity of these reactions, although steric effects (with *m*- or *p*-substituents) were also critical. The 92% e.e. achieved in the hydrogenation of 2,2,2-trifluoroacetophenone is the highest value obtained so far in this reaction using any heterogeneous catalyst system.

1. Introduction

Fluoroorganic compounds have been investigated intensively in the past decades in pharmaceutical chemistry and agrochemistry.[1] Due to their special electronic properties and hydrogen bond acceptor characteristics, fluorine atoms have frequently been placed strategically into various organic compounds in order to tune their properties and reactivities.[2] Typical biological applications are the inhibition or promotion of enzymes. Trifluoromethyl ketones and alcohols were the first synthetic inhibitors of an enzymatic process responsible for resistance to β-lactam antibiotics.[3] These compounds are also important precursors for specialty chemicals applied in electro-optic devices such as LCDs.[4]

Alongside some biological reduction methods and the application of chiral hydride reagents,[5] the asymmetric hydrogenation of trifluoromethyl ketones is one of the most useful methods for the synthesis of chiral trifluoromethyl alcohols. Homogeneous chiral transition metal catalysts perform excellently in the enantioselective hydrogenation of 2,2,2-trifluoroacetophenone and its aryl-substituted derivatives.[6,7] However, heterogeneous catalysts are less efficient: in the hydrogenation of 2,2,2-trifluoroacetophenone a cinchona-modified Pt/Al_2O_3 catalyst afforded 100% chemoselectivity to the corresponding trifluoromethyl alcohol but the e.e. was only 74%.[8–10]

The enantioselective hydrogenation of aryl-substituted trifluoroacetophenones (Scheme 1) over a chirally modified Pt catalyst represent interesting model reactions for studying the role of electronic effects on the process of enantiodifferentiation. Although it is widely accepted that the presence of an electron-withdrawing group α- to the keto carbonyl group is crucial in the



N°	X	Y
1	H	CF_3
2	H	H
3	CF_3	H
4	CH_3	H
5	$N(CH_3)_2$	H

	R	Z
CD	H	-
CD·HCl	H	HCl
MeOCD	CH_3	-

Scheme 1. Hydrogenation of aryl-substituted trifluoromethyl ketones **1**–**5** over chirally modified Pt (top), and the structures of modifiers (bottom).

* Corresponding author. Tel.: 0041 1 632 31 53; fax: 0041 1 632 11 63; e-mail: baiker@tech.chem.ethz.ch

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enantio-differentiating step,[8] the specific role of this functional group is still poorly understood. The advantage of aryl-substitution of 2,2,2-trifluoroacetophenone **2** is that the electron density at the carbonyl group can be tuned without changing the environment in the close neighborhood of the carbonyl group. Only *m*- and *p*-substituents have been chosen in order to minimize the interaction with the carbonyl group.

2. Results

Hydrogenation of various *p*- and *m*-substituted trifluoroacetophenones (Scheme 1) was catalyzed by Pt/Al_2O_3 (5% w/w), chirally modified by simple addition of a cinchona alkaloid to the reaction mixture (e.g. chinchonidine, CD). Five sets of reaction conditions have been applied by varying the chemical structure of the alkaloid, the amount and composition of the solvent, and the total pressure (Table 1). Conditions A–E are chosen on the basis of former studies of the hydrogenation of **2** where the highest e.e. was achieved in 1,2-dichlorobenzene with CD·HCl as modifier, under mass transport limited conditions.[11] The set of reaction conditions in A (Table 1) represents significant hydrogen transport limitations due to the high reactant concentration and the low pressure corresponding to low surface hydrogen concentration. In contrast, in the hydrogenation of other activated ketones over Pt high e.e.s are usually achieved in toluene with CD or MeOCD as modifiers, and by operating the reactor in the kinetic regime.[12]

The enantioselectivities in the presence of an electron-withdrawing or releasing substituent are compared to those achieved in the hydrogenation of **2**, considered as the reference reaction (Fig. 1). The e.e. increased when replacing the toluene solvent with 1,2-dichlorobenzene (conditions C→A and D→B) and replacing CD with the hydrochloride salt, CD·HCl (conditions D→C and B→A). The best e.e.s were obtained under mass transport limited conditions (A). Hydrogenation of **1** offered the highest e.e. of 78%. On the other hand, the use of MeOCD as the chiral modifier led to an almost complete loss of e.e. and even to a small e.e. (4–11%) in favor of the opposite (*S*)-enantiomeric product.

When considering only the efficient modifiers CD and CD·HCl, there is a considerable effect of the aromatic functional groups on the enantioselectivity of the reaction (Fig. 1). With CD·HCl the difference between the highest and lowest e.e.s achieved in the hydrogenation of **1** and **4**, respectively, was 26% in toluene working in the kinetic regime (C) and 48% in 1,2-dichlorobenzene under mass transport limitation (A). The enantioselectivities collected in Fig. 1 indicate that there is some predicting value of the Hammett parameters. Hydrogenation of **1** and **3**, which possess an electron-withdrawing CF_3 group ($\sigma_m=0.46$, $\sigma_p=0.53$), provides mostly higher e.e. than the hydrogenation of **4** and **5**, which contain electron-donating Me ($\sigma_p=-0.14$) and $N(Me)_2$ ($\sigma_p=-0.63$) groups, respectively.[13] A quantitative correlation between e.e. and σ is not expected as some substituents contain strongly interacting groups (H-bond acceptor, base), which can influence the reactant–modifier interactions. Furthermore, the steric needs of the substituents are different, which might affect the reactant–modifier arrangement on the Pt surface thus affecting the enantiodiscrimination. The considerable difference between **1** and **3** under all conditions may be an indication that the CF_3 substituent in *p*-position is detrimental to the reactant–modifier interaction. Finally, the better than expected enantioselectivities with unfunctionalized trifluoroacetophenone **2** is attributed to the fact that the reaction conditions A–D were chosen on the basis of former extensive studies on this reactant.[8,9] It is very likely that these conditions would not be ideal for the reactions of **1** and **3**–**5**.

The rates for all reactions in this study are collected in Fig. 2. Hydrogenation of **2** and the two reactants containing an electron-withdrawing CF_3 group (**1** and **3**) was rapid in toluene and in 1,2-dichlorobenzene in the presence of CD (conditions B–D). With MeOCD (E), and particularly under hydrogen transport limited conditions (A), the rates were generally lower. Hydrogenation of **4** and **5**, both containing an electron-donating substituent, was slow under any reaction conditions, compared to the reduction of **1**–**3**. Considering all reactants, there is qualitative agreement between the electronic nature of the substituent and the hydrogenation rate observed when using CD or CD·HCl. The rate decreased starting from **1** or **3** ($\sigma_m=0.46$, $\sigma_p=0.53$) via **2** ($\sigma=0$) to **5** ($\sigma_p=-0.63$).

In the hydrogenation of **2** further improvement was achieved in acidic medium. In contrast to an earlier report,[14] AcOH proved to be a very good solvent. Under standard conditions the e.e. doubled when toluene was replaced by AcOH ($pK_a=4.75$).[15] Trifluoroacetic acid (TFA, $pK_a=0.3$)[15] was more effective, already small amounts (TFA/CD = 9.6 mol/mol) increased the e.e. to 88% in toluene under standard conditions. Further variation of temperature and reactant concentration provided 92% e.e. (Table 2). This is the best value reported to date for the enantioselective hydrogenation of this compound over a heterogeneous catalyst.

Table 1. Reaction conditions for the hydrogenation of reactants 1–5[a]

Conditions	Modifier	Solvent (mL)	Pressure (bar)
A	CD·HCl	1,2-Dichlorobenzene (1)	2
B	CD	1,2-Dichlorobenzene (5)	10
C	CD·HCl	Toluene (5)	10
D	CD	Toluene (5)	10
E	MeOCD	Toluene (5)	10

[a] Common conditions: 5 wt% Pt/Al_2O_3 (42±2 mg), modifier (6.8 μmol), reactant (1.85 mmol) (reactant/modifier = 272 mol/mol), room temperature.

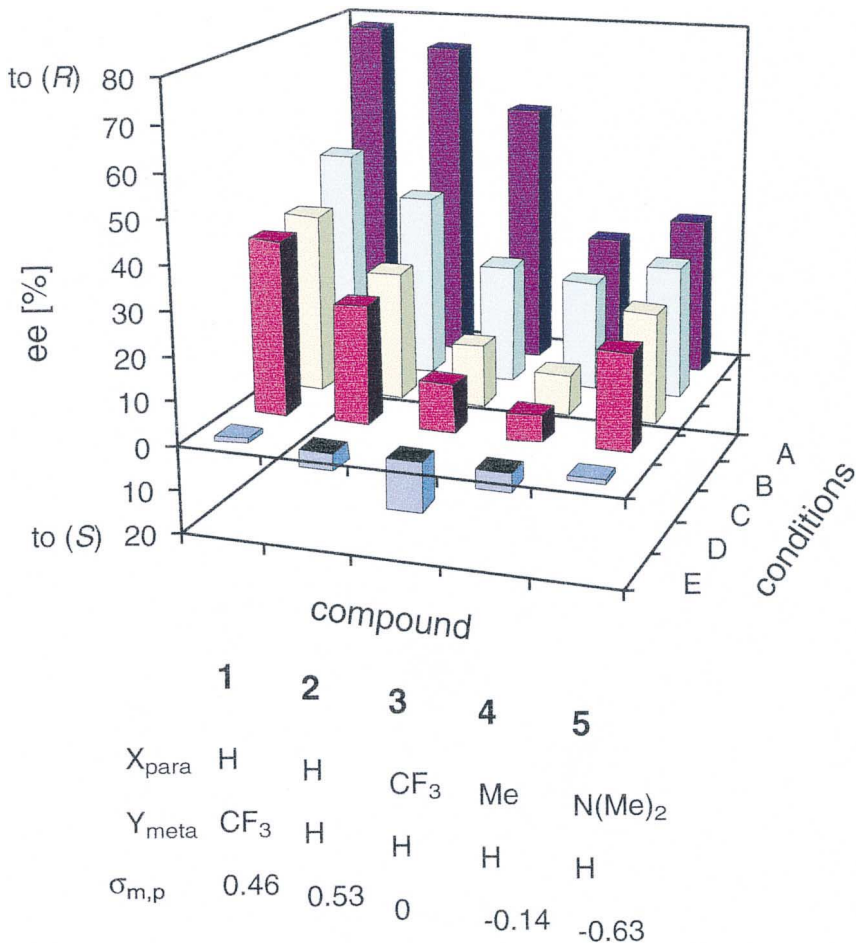


Figure 1. Enantioselectivities obtained in the hydrogenation of substituted trifluoromethyl ketones in toluene or 1,2-dichlorobenzene with three different modifiers. The electronic nature of the substituents is illustrated by the σ values. The structures of reactants and modifiers are given in Scheme 1. For the reaction conditions see Table 1.

The effect of adding carboxylic acids on the enantioselectivity strongly depended on the substrate structure. With **3** and **5** the e.e. was considerably lower in acidic medium, compared to the best value achieved under conditions A. For comparison, replacing CD with CD·HCl (Fig. 1, conditions A and B) always increased the e.e. Obviously, the effect of carboxylic acids cannot be attributed only to protonation of the quinuclidine nitrogen atom. Probable reasons for this deviation are the interaction of the strong H-bond acceptor substituents in **1**, **3** and **5** with the carboxylic acid, and the change of the σ value by protonation of the $N(Me)_2$ group. The strong interaction of CD with carboxylic acids[16] and its implication to the reaction mechanism will be discussed elsewhere.

The highest enantioselectivities achieved in this limited parameter study (focusing exclusively on the effect of solvent, acid additive and reactant concentration) are presented in Table 2. The *m*-CF_3 substituted derivative **1** afforded more than 80% e.e. indicating the positive effect of an electron-withdrawing substituent in the *m*-position. It is probable that systematic optimization of the reaction conditions will lead to further improvements in the hydrogenation of **1** and **3**–**5**.

3. Discussion

The remarkable similarities in the effect of the reaction conditions in the hydrogenation of **1**–**5** (stepwise decrease in e.e. from conditions A to E, Fig. 1) is an indication, that in weakly polar medium all these substituted trifluoroacetophenones are transformed to the corresponding chiral alcohols via the same reaction pathway and mechanism. In particular, the nature of reactant–modifier interaction is assumed to be the same for all reactants. Special interactions between reactant and modifier, involving the heteroatoms of the substituents {e.g. CF_3 or $N(Me)_2$} as additional interaction sites, have only minor influence in toluene and 1,2-dichlorobenzene. We propose that the observed differences in enantioselection are due to variations in the electron density at the carbonyl group, induced by the aromatic substituents.

The results in the hydrogenation of **1** and **3** also show a considerable steric effect. Under certain conditions the influence of substituent position (*m* or *p*) is comparable to the electronic effect characterized by the Hammett constant (see Fig. 1). Generally, the hydrogenation of *p*-substituted reactants provided lower

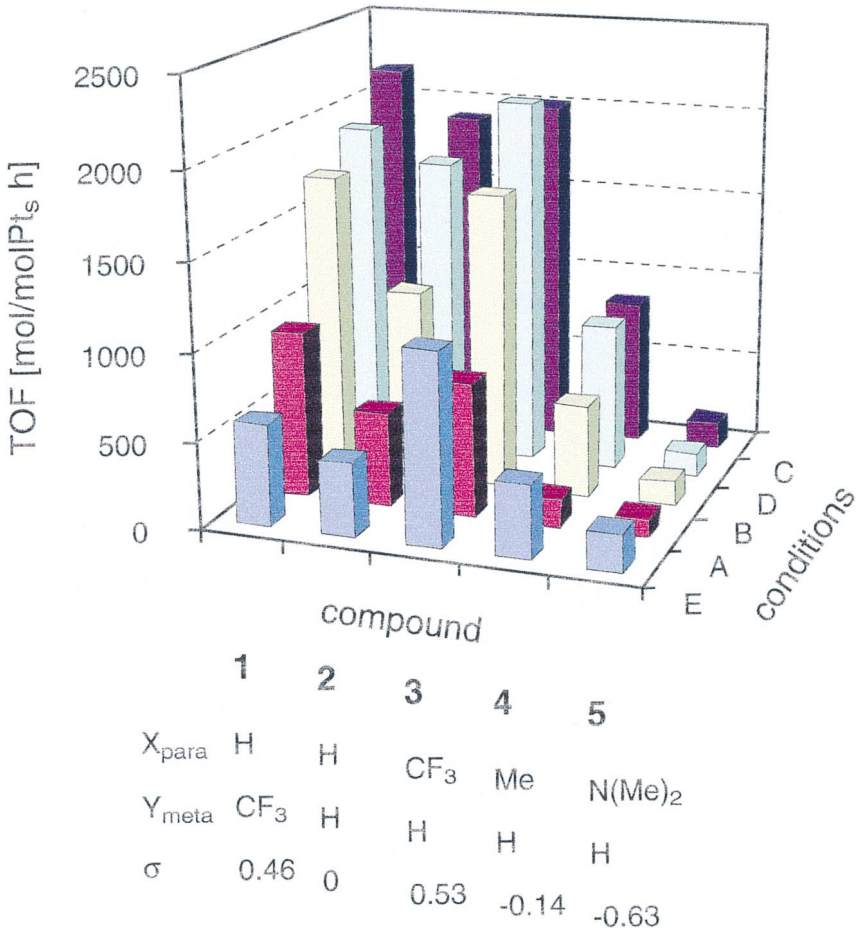


Figure 2. Average reaction rates (TOFs) in the hydrogenation of substituted trifluoromethyl ketones in toluene or 1,2-dichlorobenzene with three different modifiers. The structures of reactants and modifiers are given in Scheme 1. For the reaction conditions see Table 1.

enantioselectivity than that of the reference reactant **2** and the *m*-substituted compound **1**. Still, among the *p*-substituted compounds a qualitative agreement between the σ values and the e.e. implies that lower electron density at the carbonyl group of the reactant improves the enantioselection. This conclusion is in agreement with our earlier suggestion that activation of the keto-carbonyl group is required to obtain good enantioselectivity in the enantioselective hydrogenation over chirally modified Pt.[8] Furthermore, the positive correlation between the σ values and the hydrogenation rates (Fig. 2) shows that activation of the ketone enhances also the reaction rates.

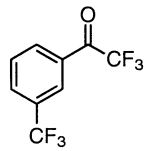
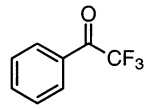
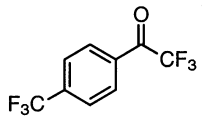
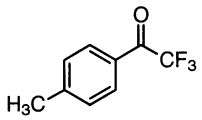
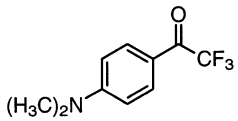
The very low e.e. values and TOF's obtained with all reactants when using MeOCD as modifier is a strong indication that the OH group of CD is involved in the process of enantiodiscrimination. We have shown earlier that methylation of the quinuclidine nitrogen of CD leads to a complete loss of enantioselectivity.[11] Obviously, in the hydrogenation of trifluoroacetophenones over cinchona-modified Pt, both the quinuclidine nitrogen and the hydroxyl functions are crucial to enantiodifferentiation. In contrast, for the thoroughly investigated hydrogenation of α-keto esters it is assumed that the hydroxyl group is not involved in the reactant–modifier interaction and enantiodiscrimination is attributed to a single attractive interaction (N–H–O type hydrogen bond) between the CD and the ketone and to some additional steric repulsion between the two molecules.[17,18]

4. Conclusions

Hydrogenation of 2,2,2-trifluoroacetophenone **2** over cinchona-modified Pt under mild conditions afforded 92% e.e. and 100% yield within 1.5 h (TOF = 1270). This reaction is among the few examples where heterogeneous catalysis is comparable to the best homogeneous catalyst systems. The inherent advantages of the method, the commercially available catalyst and modifier as well as the easy separation of catalyst and product, makes this reaction an interesting alternative to other reduction methods.

The present study provides some insight into the role of steric and electronic effects of the aryl-substituents on the level of enantiodiscrimination in these reductions. Hydrogenation of trifluoroacetophenones possessing an electron-withdrawing substituent in the *m*-position is rapid and affords good enantioselectivities over cin-

Table 2. The best enantioselectivities obtained with substituted trifluoromethyl ketones 1–5 over CD-modified Pt. Conditions that are not specified here are set according to the standard reaction procedure

Compound	No.	Amount (mmol)	Solvent	TFA/React. (mol/mol)	TOF[a]	E.e. (%)
	**1**	3.69	Toluene	19.2	635	81
	**2**	5.54	Toluene	9.6	1270	92[b]
	**3**	1.85	1,2-Dichlorobenzene	–	762	60[c]
	**4**	1.85	Acetic acid	76.8	66	46
	**5**	1.85	1,2-Dichlorobenzene	–	111	36[c]

[a] (mol/mol Pt_s, h).
[b] At 0°C.
[c] Mass transport limited conditions (A): 1 mL solvent, 2 bar pressure, CD·HCl (see Table 1).

chona-modified Pt. Hence, future work will be driven in this direction.

5. Experimental

4′-(Dimethylamino)-2,2,2-trifluoroacetophenone (Aldrich, 97%) was purified by filtration through silica gel 60 (Fluka). All other chemicals and catalyst were used as received. For some reactions high purity TFA (Fluka, for UV spectroscopy, >99%) was used. MeOCD was synthesized as described before.[19] 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. The metal dispersion after heat treatment was 0.27, as determined by transmission electron microscopy.

Hydrogenations were carried out at rt in an autoclave equipped with a 50 mL glass liner and a PTFE cover, and with magnetic stirring (1000 rpm). Total pressure and H_2 uptake were controlled by a computerized constant volume constant pressure equipment (Büchi BPC 9901).

Under *standard conditions* the catalyst (42±2 mg) was added to a mixture of modifier (6.8 μmol) and reactant (1.85 mmol) in solvent (5 mL) and the hydrogenation reaction was carried out at 10 bar until H_2 consumption ceased (or for a maximum of 2 h.).

Conversions and enantioselectivities were determined by direct gas chromatographic analysis of the reaction mixture, using a Chirasil-DEX CB (Chrompack 7502, 25 m×0.25 mm×250 nm) capillary column in an HP 6890 gas chromatograph. For all reactants baseline separation was achieved. Conditions: split injection (250°C, 1:20), He carrier gas (50 cm s^{-1}), FID detector (275°C), 100–150°C column temperature. In the hydrogenation of **2**, CD and CD·HCl always provided the (*R*)-enantiomer of the chiral alcohol product in excess.[8] On the basis of the analogous separation of the products we assumed that also in the hydrogenation of **1** and **3**–**5** the (*R*)-enantiomer formed in excess with these

modifiers. Average reaction rates (TOFs) were calculated based on the time needed to obtain at least 95% conversion and are related to the number of surface Pt atoms (Pt_s). The estimated standard deviations are less than ±0.5% for e.e. and ±5–10% for TOF (the lower values are related to the slower reactions).

Acknowledgements

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