Enantioselective hydrogenation of trifluoroacetophenone over cinchonidine-modified platinum

Tamas Mallat, Michael Bodmer and Alfons Baiker

Department of Chemical Engineering and Industrial Chemistry, Swiss Federal Institute of Technology, ETH Zentrum, CH-8092 Zurich, Switzerland

Received 23 August 1996; accepted 3 December 1996

The enantioselective hydrogenation of 2,2,2-trifluoroacetophenone to (R)-1-phenyl-2,2,2-trifluoroethanol represents a new application of supported Pt catalysts modified with cinchona alkaloids. Heat treatment of a 5 wt% Pt/alumina catalyst at 400°C in flowing hydrogen, followed by an air-treatment of the reaction mixture before the hydrogenation reaction improved the enantiomeric excess by a factor of 2.5. Traces of water in apolar medium, high trifluoroacetophenone and moderate cinchonidine concentrations were also advantageous for enantiodifferentiation. Both reaction rate and enantiomeric excess increased during the initial transient period of the reaction, below 10% conversion.

Keywords: enantioselective hydrogenation, trifluoroacetophenone, Pt/alumina, cinchonidine

1. Introduction

The most successful strategy of preparing solid asymmetric hydrogenation catalysts is the modification of known metal catalysts, such as platinum or nickel, by strongly adsorbed chiral compounds of natural origin [1–4]. The Pt/cinchona alkaloid system provided enantiomeric excesses (ee's) up to 85–95% in the partial hydrogenation of α-ketoacids and α-ketoesters [5,6]. Even a few years ago this catalyst system was considered as extremely specific (almost enzyme-like): any change in the catalytically active metal, the chiral auxiliary or the reactant resulted in a considerable or complete loss of enantioselection.

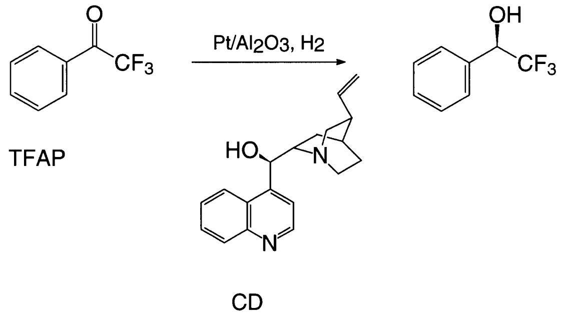
It has been shown recently that not only cinchona alkaloids but also structurally simple chiral amines and amino alcohols [7–11], and a vinca-type alkaloid [12,13] are efficient modifiers of Pt in the enantioselective hydrogenation of ethyl pyruvate.

In the late eighties several efforts have been made to broaden the application range of cinchona-modified Pt, without a resounding success. Only 5–12% ee was obtained in the enantioselective hydrogenation of arylalkyl ketones, α-methoxy ketones and β-diketones [14]. The highest ee reported to date in the hydrogenation of a β-ketoester (methyl acetoacetate) is 20%, using a cinchonine-modified Pt/polystyrene catalyst [15]. Recently, 33–38% ee has been obtained in the hydrogenation of α-diketones to (R)-hydroxyketones over Pt/silica modified with cinchonidine [16]. Here, we report the successful hydrogenation of another type of α-substituted carbonyl compound, 2,2,2-trifluoroacetophenone (TFAP) over Pt/alumina modified with cinchonidine (CD), as shown in scheme 1.

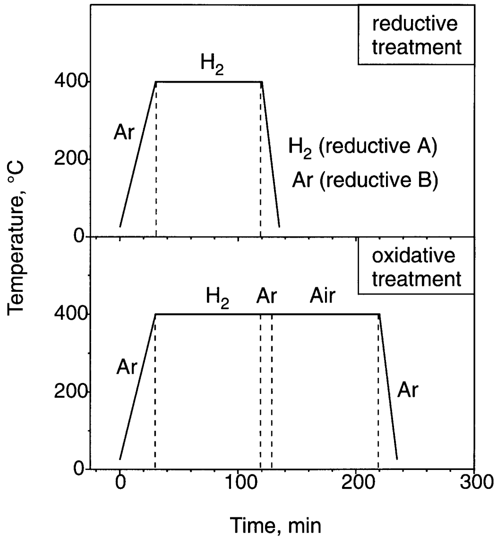
2. Experimental

A 5 wt% Pt/alumina catalyst (Engelhard 4759) was used for all experiments. The metal dispersion before and after reductive heat treatment "A" was 0.38 and 0.27, respectively, as calculated from TEM images [17]. The BET surface area of the catalyst was 125 $m^2\ g^{-1}$. Heat treatment was performed in a fixed-bed reactor by exposing the catalyst to 15–30 ml min^{-1} Ar, H_2 or air. Catalyst temperature and gas composition during reductive and oxidative treatments are shown in scheme 2.

Hydrogenations were performed in a 100 ml stainless steel autoclave (Baskerville) with magnetic stirring ($n = 1000\ min^{-1}$). A 50 ml glass liner with a PTFE cap and stirrer was used to keep the system inert. Under standard conditions, 90 ± 2 mg 5 wt% Pt/alumina (after reductive treatment A, scheme 2), 1.28 g (7.35 mmol) 2,2,2-trifluoroacetophenone (TFAP, Fluka), 13.6 μmol cinchonidine (CD, Fluka) and 20 ml solvent (puriss grade, > 99%) were mixed under air for



Scheme 1.



Scheme 2.

20 min before reaction (in the glass liner of the autoclave). The hydrogenation reaction was carried out at room temperature (20–22°C) and 10 bar pressure. The pressure was hold at a constant value by a computerized constant volume–constant pressure equipment (Büchi BPC 9901).

The enantiomeric excess (ee) and conversion were determined by an HP 5890A gas chromatograph with a Chirasil DEX CB (Chrompack) capillary column. The standard deviation of the analytical method was ±0.5%. The enantioselectivity is expressed as ee (%) $= 100 \times |([R] - [S])|/([R] + [S])$.

3. Results

3.1. *Influence of catalyst pretreatment*

The saturation of the carbonyl group of 2,2,2-trifluoroacetophenone (TFAP) runs smoothly even at low pressures to the corresponding trifluoromethyl benzyl alcohol; no byproducts were detected by GC analysis. The ee to the (R)-enantiomer was rather poor when using CD and a 5 wt% Pt/alumina without any pretreatment (i.e. stored in air in a closed vessel).

As illustrated in scheme 2 and table 1 (entries 1–3), reductive pretreatment in flowing hydrogen at 400°C [3] increased the ee from 16 to over 30%. TEM investigations revealed that during heat treatment in hydrogen the average particle size of Pt increased and the dispersion decreased by 30–40 (relative) %.

Cooling the catalyst after heat treatment in hydrogen (“reductive A”) or nitrogen (“reductive B”) afforded about the same ee, but the reaction was faster when hydrogen was used during cooling (table 1, entries 2 and 3). A reductive pretreatment at 400°C, followed by oxidation with air at the same temperature lowered the ee, without influencing the reaction time necessary for 90–95% conversion (table 1, entries 4 and 5). Accordingly, the “reductive A” method was used later as a standard procedure.

When the reaction mixture (containing the prereduced catalyst, modifier, reactant and solvent) was mixed in air before the hydrogenation reaction, the ee improved further by 7%, as shown in table 2. This treatment had only minor influence on the reaction rate determined from the initial or the average rate of hydrogen consumption.

Data in tables 1 and 2 indicate that oxygen should be avoided during heat treatment of the catalyst at high temperature, but oxidation of the catalyst surface at room temperature is advantageous for enantioselection. A possible explanation for the latter is that during stirring in air the Pt surface is oxidized to PtO_x, and the surface oxide is re-reduced to Pt^0 active sites at the beginning of the reaction. The simultaneously formed water is adsorbed on the catalyst surface and changes the environment of the active sites. In control experiments, small amounts of water were injected into the reaction mixture after stirring in air and before the hydrogenation reaction. Fig. 1 shows that the addition of up to 25 mg water to the toluenic solution slightly increased the ee. Above the optimum amount of water the ee dropped rapidly, probably due to phase separation. The initial rate of hydrogen consumption increased moderately (by a factor of 1.2) after addition of 25 mg water, but decreased drastically (by a factor of 25) in the presence of 75 mg water. Note that other effects, such as the oxidative removal of some surface impurities from the catalyst during mixing in air in the apolar solvent, could also have contributed to the observed increase (by 7%) of ee.

Table 1
Influence of catalyst pretreatments, shown in scheme 2 (90 mg 5 wt% Pt/alumina, 1.28 g TFAP, 10 bar, 20°C)

No.	Pretreatment	Solvent	CD (mg)	Time (min)	Conv. (%)	ee (%)
1	–	toluene	2	63	89	16
2	reductive A	toluene	2	50	96	33
3	reductive B	toluene	2	86	95	33
4	reductive A	1,2-dichlorobenzene	4	105	95	45
5	oxidative	1,2-dichlorobenzene	4	105	91	29

Table 2
Influence of stirring the reaction mixture in air for 20 min after "reductive A" catalyst pretreatment and before the hydrogenation reaction (90 mg 5 wt% Pt/alumina, 4 mg CD, 1.28 g TFAP, 20°C)

Stirring in air [a]	Solvent	Pressure (bar)	r^0 (ml H_2 min^{-1})	Time (min)	Conv. (%)	ee (%)
−	toluene	10	12	50	96	33
+	toluene	10	10	60	100	40
−	1,2-dichlorobenzene	1	1.8	120	98	42
+	1,2-dichlorobenzene	1	2.1	120	99	49

[a] + and − indicate with or without aerobic pretreatment, respectively.

3.2. Influence of modifier concentration

The strong dependence of ee on the modifier concentration is illustrated in fig. 2. Maximum ee was achieved with a CD : TFAP molar ratio of 1 : 540. The average reaction rate, calculated from the reaction time necessary for 50% conversion, was 3.5 times higher at this modifier concentration, compared to the rate of racemic hydrogenation. The rate acceleration due to the presence of a chiral modifier was reported to be considerably higher (up to a factor of 20) in the enantioselective hydrogenation of ethyl pyruvate over supported Pt catalysts [9,11,13,18,19].

3.3. Initial transient period

Analysis of the initial transient period of the reaction revealed that both the reaction rate and the ee increase with time, as shown in fig. 3. This effect is limited to the beginning of the reaction.

A feasible explanation is that the enantioselectivity of chirally modified Pt develops gradually. Before the hydrogenation starts, the Pt surface is in an oxidized state. Hydrogen rapidly reduces PtO_x to Pt^0 (active site) and adsorbs on the metal surface. Parallel to this reduction, the adsorption of CD, TFAP and solvent changes substantially. The proper adsorption of modifier on the Pt surface increases the ee and also the reaction rate as indicated by the enhanced rate of TFAP conversion. The steady-state conditions are seemingly achieved after about 20 min (10% conversion). A similar phenomenon has been observed previously in the enantioselective hydrogenation of ethyl pyruvate [21,22].

However, both conversion and ee are integral values. The real length of the transient period can only be determined from the differential (incremental) values. The incremental ee (ee_{inc}) and reaction rate as a function of TFAP conversion are shown in fig. 4. After about 2% conversion the difference between the ee_{inc} and the final (integral) ee was smaller than the standard deviation of the analytical method. Interestingly, the reaction rate still increased when the ee had already reached its final, steady-state value. A more detailed investigation is required in the future to reveal the influence of catalyst pretreatment and reaction conditions on the nature of the initial transient period.

The above results suggests that the final ee should increase when the influence of the initial transient period is negligible. The increase of ee with increasing reactant concentration, reaching a plateau above 1 mol ℓ^{-1}, sup-

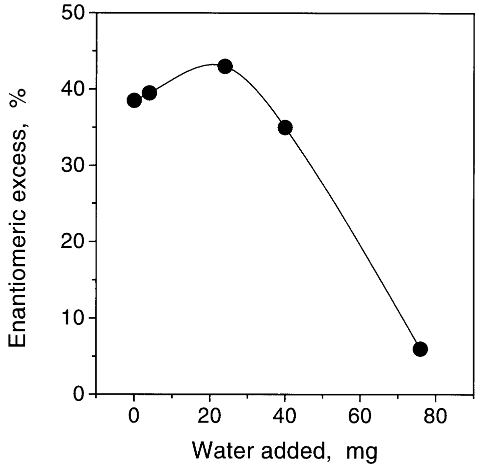


Fig. 1. Influence of water injected into the reaction mixture after catalyst prereduction at 400°C and stirring the reaction mixture in air at room temperature (90 mg 5 wt% Pt/alumina, standard pretreatment, 1.28 g TFAP, 4 mg CD, 20 ml toluene, 10 bar, 20°C).

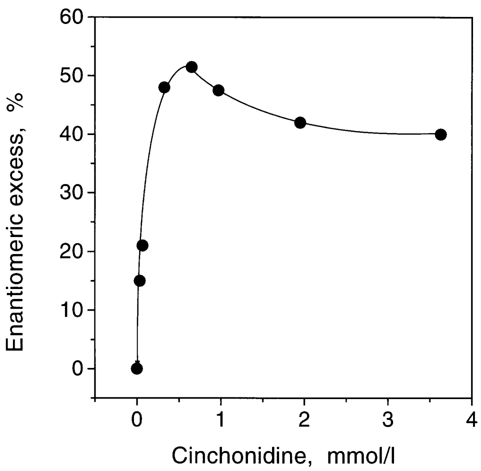


Fig. 2. Influence of modifier concentration on the enantiomeric excess (90 mg 5 wt% Pt/alumina, standard pretreatment, 1.28 g TFAP, 20 ml 1,2-dichlorobenzene, 10 bar, 20°C).

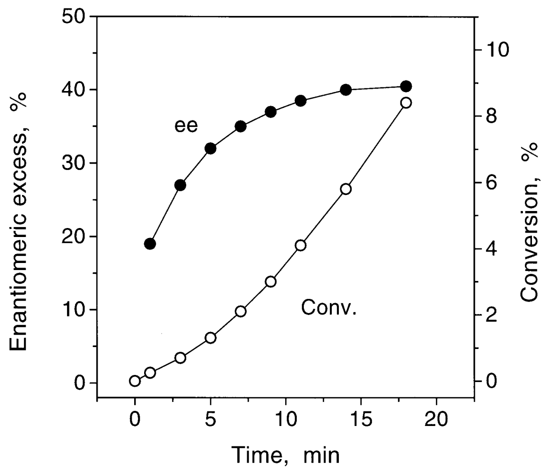


Fig. 3. Correlation between enantiomeric excess and conversion (90 mg 5 wt% Pt/alumina, standard pretreatment, 1.28 g TFAP, 4 mg CD, 20 ml 1,2-dichlorobenzene, 1 bar, 22°C).

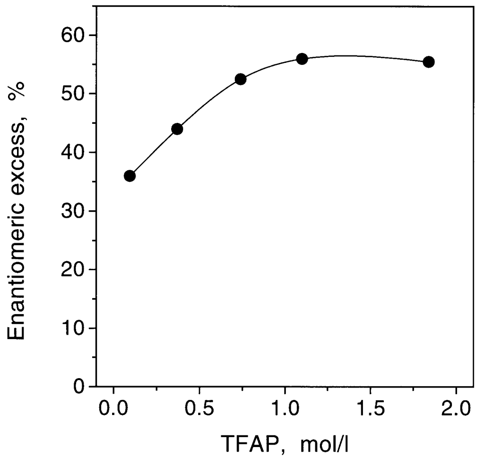


Fig. 5. Influence of initial reactant concentration on the enantiomeric excess (90 mg 5 wt% Pt/alumina, standard pretreatment, 1.28 g TFAP, 4 mg CD, 20 ml 1,2-dichlorobenzene, 10 bar, 20°C).

ports this assumption (fig. 5). In the region of the plateau the modifier : reactant molar ratio corresponds to 1 : (1600–2700).

4. Discussion

Our study indicates that the application range of Pt catalysts modified by cinchona alkaloids may be considerably broader than expected a few years ago. It was not clear until now which requirements the reactant has to fulfill for obtaining good ee: the two carbonyl groups in α,β position (α-ketoesters, α-ketoacids and α,β-diketones) and adsorbed parallel to the Pt surface in trans position, or a carbonyl group activated by an electron-withdrawing group in α-position. Our results provide evidence for the latter. A comparison of the enantioselective hydrogenation of some aromatic carbonyl compounds, shown in table 3, indicates that medium to good ee can be achieved only in the presence of an electron-withdrawing group in α-position (ester, carboxyl and trifluoromethyl groups). There is hardly any enantiodifferentiation detectable for acetophenone (electron-releasing methyl group).

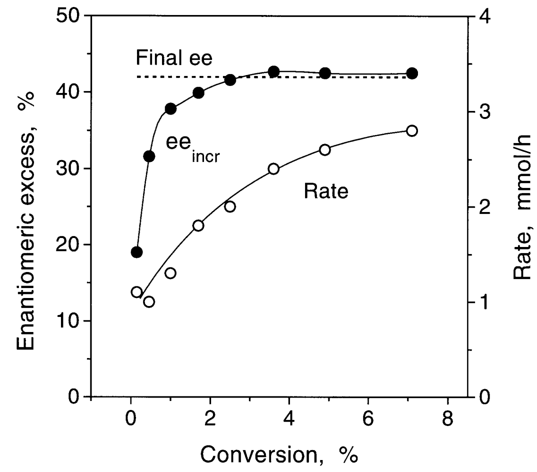


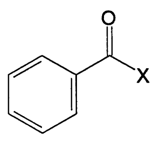
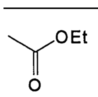
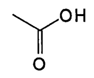
Fig. 4. Incremental enantiomeric excess (ee_{inc}) and reaction rate during the initial transient period, and the final enantiomeric excess at full conversion (for conditions see fig. 3).

The enantiomeric excesses reported are not optimized values; it is likely that the study of the influence of other parameters in the hydrogenation of TFAP will result in a further enhancement of enantiodifferentiation.

Acknowledgement

Financial support of this work by the Swiss National Science Foundation (Program CHiral 2) is gratefully acknowledged.

Table 3
The influence of the substituent X in α-position to the carbonyl group of some simple aromatic ketones on the enantomeric excess

	X	ee (%)
		89.5 [a]
		51 [b]
	–CF_3	56 [c]
	–CH_3	2–3 [c]

[a] For conditions see ref. [20].

[b] For conditions see ref. [5].

[c] Conditions: 90 mg 5 wt% Pt/alumina, standard pretreatment, 3.8 g reactant, 4 mg CD, 20 ml 1,2-dichlorobenzene, 10 bar, 20°C.

References

[1] D. Lipkin and T.D. Stewart, J. Am. Chem. Soc. 61 (1939) 3295.

[2] Y. Nakamura, Bull. Chem. Soc. Japan 16 (1941) 367.

[3] Y. Orito, S. Imai and S. Niwa, J. Chem. Soc. Japan (1979) 1118.

[4] Y. Izumi, Adv. Catal. 32 (1983) 215.

[5] H.U. Blaser and H.P. Jalett, Stud. Surf. Sci. Catal. 78 (1993) 139.

[6] H.U. Blaser, H.P. Jalett and J. Wiehl, J. Mol. Catal. 68 (1991) 215.

[7] G. Wang, T. Heinz, A. Pfaltz, B. Minder, T. Mallat and A. Baiker, J. Chem. Soc. Chem. Commun. (1994) 2047.

[8] K.E. Simons, G. Wang, T. Heinz, T. Giger, T. Mallat, A. Pfaltz and A. Baiker, Tetrahedron: Asym. 6 (1995) 505.

[9] B. Minder, T. Mallat, A. Baiker, G. Wang, T. Heinz and A. Pfaltz, J. Catal. 154 (1995) 371.

[10] T. Heinz, G. Wang, A. Pfaltz, B. Minder, M. Schürch, T. Mallat and A. Baiker, J. Chem. Soc. Chem. Commun. (1995) 1421.

[11] B. Minder, M. Schürch, T. Mallat, A. Baiker, T. Heinz and A. Pfaltz, J. Catal. 160 (1996) 261.

[12] A. Tungler, T. Tarnai, T. Màthé, G. Vidra, J. Petrò and R.A. Sheldon, in: *Catalysis of Organic Reactions*, eds. M.G. Scaros and M.L. Prunier (Dekker, New York, 1995) p. 201.

[13] A. Tungler, T. Màthé, K. Fodor, R.A. Sheldon and P. Gallezot, J. Mol. Catal. 108 (1996) 145.

[14] H.U. Blaser, H.P. Jalett, D.M. Monti, J.F. Reber and J.T. Wehrli, Stud. Surf. Sci. Catal. 41 (1988) 153.

[15] S. Bhaduri, V.S. Darshane, K. Sharma and D. Mukesh, J. Chem. Soc. Chem. Commun. (1992) 1738.

[16] W.A.H. Vermeer, A. Fulford, P. Johnston and P.B. Wells, J. Chem. Soc. Chem. Commun. (1993) 1053.

[17] T. Mallat and J. Petro, React. Kinet. Catal. Lett. 11 (1979) 307.

[18] M. Garland and H.U. Blaser, J. Am. Chem. Soc. 112 (1990) 7048.

[19] G. Bond, P.A. Meheux, A. Ibbotson and P.B. Wells, Catal. Today 10 (1991) 371.

[20] S. Niwa, S. Imai and Y. Orito, J. Chem. Soc. Japan (1982) 137.

[21] U.K. Singh, R.N. Landau, Y. Sun, C. LeBlond, D.G. Blackmond, S.K. Tanielyan and R.L. Augustine, J. Catal. 154 (1995) 91.

[22] J. Wang, Y. Sun, C. LeBlond, R.N. Landau and D.G. Blackmond, J. Catal. 161 (1996) 752.