Highly efficient platinum-catalyzed enantioselective hydrogenation of trifluoroacetoacetates in acidic solvents

M. von Arx, T. Mallat, and A. Baiker

Labratory of Technical Chemistry, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich, Switzerland
E-mail: baiker@tech.chem.ethz.ch

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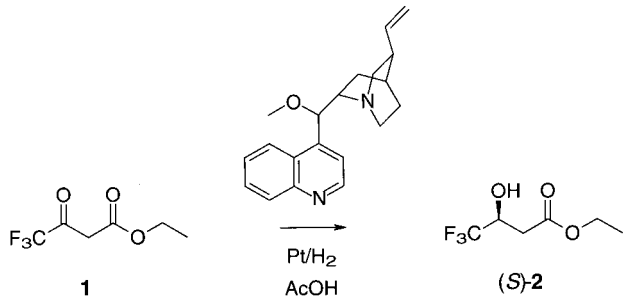
The hydrogenation of methyl-, ethyl- and isopropyl-4,4,4-trifluoroacetoacetates to the corresponding chiral trifluoromethyl alcohols has been investigated over Pt/Al_2O_3 modified by *O*-methyl-cinchonidine. Up to 96% ee and 1850 h^{-1} average TOF have been achieved in the synthesis of this important chiral building block. The special role of reaction medium and particularly the impact of water and acids on enantiodiscrimination are discussed.

KEY WORDS: enantioselective; hydrogenation; α,α,α-trifluoromethyl ketone; solvent effect; Pt/alumina; trifluoroacetic acid; cinchona alkaloids

1. Introduction

Cinchona alkaloid-modified Pt, together with the Ni-tartrate system, is the most promising heterogeneous enantioselective catalyst for the preparation of chiral compounds with high optical purity [1–6]. A recent extension of the application range of Pt is the hydrogenation of various α,α,α-trifluoromethyl ketones to the corresponding alcohols [7–9]. Up to 90% ee was achieved in the transformation of ethyl-4,4,4-trifluoroacetoacetate **1** (Scheme 1) in acetic acid in the presence of *O*-methyl cinchonidine (MeOCD) as chiral modifier. The produced α,α,α-trifluoromethyl alcohol **2** represents an important chiral building block for the synthesis of various biologically relevant compounds [10–12]. Other methods, such as reduction of the ketone by hydridic reagents or enzymatic processes [12,13], have shown clear disadvantages with respect to selectivity, productivity and simplicity, compared to the use of chirally modified Pt. Although a few homogeneous transition metal catalysts have been tested in the hydrogenation of chiral trifluoromethyl ketones, they were not efficient in the hydrogenation of **1** [14].



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

Recently, Kuroki *et al.* [15] achieved 91% ee by using a rhodium–amidephosphine–phosphinite complex, though the (average) reaction rate was moderate (TOF: 10 h^{-1}).

Here we report some new observations in the enantioselective hydrogenation of **2** over cinchona-modified Pt. Special emphasis is put on the solvent effects and the role of acids.

2. Experimental

Ethyl-4,4,4-trifluoroacetoacetate (**1**), methyl-4,4,4-trifluoroacetoacetate (**4**) and isopropyl-4,4,4-trifluoroacetoacetate (**5**) (Fluka, purum) were distilled before use. *O*-methyl cinchonidine was synthesized according to a former recipe [16]. The solvents were dried as follows: hexane and DMF were stored over molecular sieve 3A; THF was refluxed over K and then distilled; ethanol, 2-propanol and toluene were refluxed over Na and then distilled. 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. (Note that *in situ* reduction of oxidized Pt would produce water on the metal surface.) Pt dispersion after heat treatment was 0.27 as determined by TEM.

Hydrogenations were carried out in a stainless steel autoclave equipped with a 50 ml glass liner and a PTFE cover. Efficient magnetic stirring (1000 rpm) was applied to avoid hydrogen transport limitation in the slurry reactor. Total pressure and hydrogen uptake were controlled by a computerized constant volume constant pressure equipment (Büchi BPC 9901). According to the *general reaction procedure*, 42 ± 2 mg catalyst

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was added to a mixture of 2.1 mg (6.8 μmol) MeOCD and 1.85 mmol reactant in 5 ml solvent, and the reaction was carried out at 10 bar and room temperature. For low temperature experiments the value indicates the temperature of the cryostate bath. Before starting the reaction, the reactor was equilibrated in the bath for 20 min.

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 (%) $= 100 \times |(R - S)|/(R + S)$. Average reaction rates (TOFs) were calculated based on the time needed to obtain full conversion and the number of surface Pt atoms (Pt_s). No catalyst deactivation was observed under any conditions.

NMR spectra were recorded on Bruker DPX 200 and DPX 300 spectrometers. Sample concentrations mimicked the conditions in the general reaction procedure. Relative amounts of the different compounds were calculated by integration of the peak areas in the ^{19}F spectra.

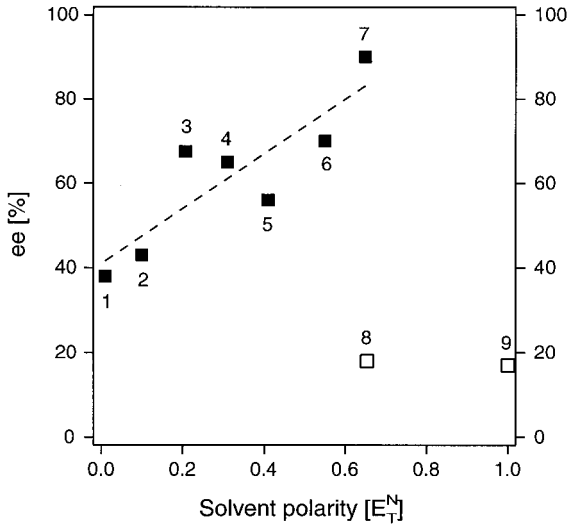


Figure 1. Relationship between the empirical solvent parameter E_T^N and enantiomeric excess (ee) in the hydrogenation of **1** over MeOCD-modified Pt under standard conditions. Solvents: hexane (1); toluene (2); THF (3); dichloromethane (4); dimethylformamide (5); 2-propanol (6); acetic acid (7); ethanol (8); and water (9).

3. Results

3.1. Influence of solvent polarity

The enantioselective hydrogenation of **1** has been studied over a 5 wt% Pt/alumina modified by *O*-methyl cinchonidine, which derivative was found to be the best modifier for this reaction [9]. Preliminary screening of the influence of various reaction parameters including reactant, modifier and catalyst concentrations, pressure and temperature revealed that the enantioselectivity is controlled mainly by the solvent composition. There is more than five-fold increase in ee observed when changing from the worst solvent, water, to the best solvent, AcOH. The picture is even more interesting when plotting the enantioselectivity as a function of Reichardt's empirical solvent parameter E_T^N [17] (figure 1). At first sight there is no clear correlation between ee and solvent polarity but a closer inspection reveals that in some solvents the low ee is due to side reactions. Water and small chain primary alcohols react with **1** and form the corresponding hydrate and hemiketal, respectively [18,19]. Hydrogenolysis of these intermediates provides **2** in low or negligible ee. Excluding those solvents where the reaction mechanism changes (open squares in figure 1), there is a clear positive correlation between solvent polarity and ee. We have repeated the experiments by replacing MeOCD by CD and the correlation between ee and E_T^N was very similar, though the enantioselectivities were lower by 5–20%.

This tendency contrasts to former observations in the hydrogenation of activated ketones such as α-ketoesters on cinchona-modified Pt, where the ee decreased with increasing solvent polarity, only AcOH being an exception [20–22]. The exceptional behaviour of AcOH has been attributed to protonation of the quinuclidine N of CD, which favors enantiodifferentiation [22,23]. In the hydrogenation of **1** the enantioselectivity in AcOH fits well into the general solvent effect.

Changing the solvent polarity by gradually replacing toluene by acetic acid increased the ee monotonously. The saturation type curve in figure 2 shows that small amounts of acetic acid cannot induce the full beneficial effect. Addition of 2 molar equivalents of acetic acid (corresponding to 0.008 vol% AcOH in figure 2) is sufficient to protonate the quinuclidine N of CD [22] (or more precisely: to form an H-bond in the apolar medium) but its effect on the ee is negligible. Obviously, in the hydrogenation of **1** the solvent properties of acetic acid are important, not the protonation of the modifier.

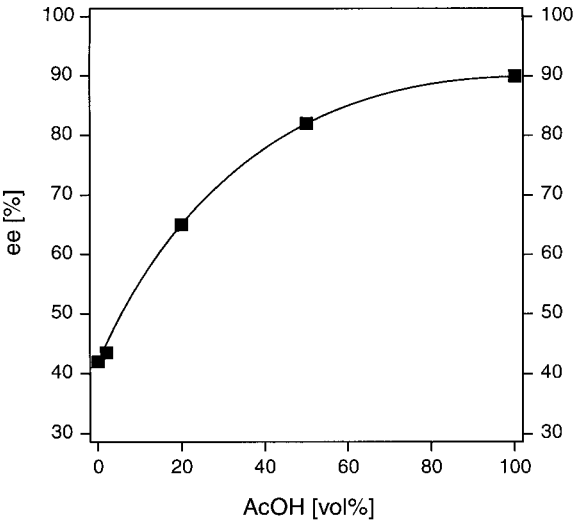


Figure 2. Change in the enantioselectivity by addition of AcOH to toluene while maintaining a constant total solvent volume of 5 ml; standard conditions.

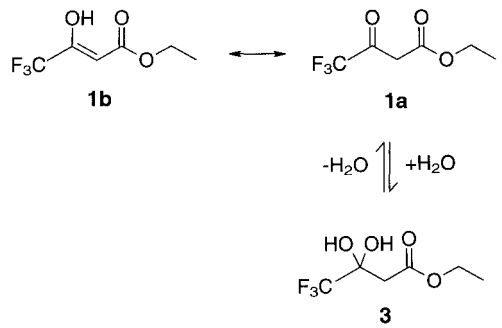
3.2. Hydrate hydrogenolysis in acetic acid

We have recently reported [18] that in the presence of even small amounts of water in THF the rate and enantioselectivity in the hydrogenation of **1** drops due to hydrate (**3**) formation (Scheme 2) and its subsequent hydrogenolysis to **2**. Extending these investigations we have found a similar behavior in other water-miscible solvents. In contrast, the ee remained constant in AcOH up to relatively high water concentration (figure 3).

The differences between the hydration of **1** in AcOH and in THF are illustrated in figure 4. In AcOH the equilibrium concentration of the ketone (**1a**) is 5.2% compared to 0.9% in THF, and the hydrate concentration is lower (80% in AcOH compared to 95.5% in THF, reached after approximately 8 h). In addition, there is a dramatic difference in the rate of equilibration. Equilibration is more than 20-fold faster in AcOH, which solvent acts also as an acid catalyst. Hydrogenation of the ketone (**1a**) over Pt is much faster than hydrogenolysis of the hydrate [18,24]. As a result, hydrate hydrogenolysis contributes to the formation of **2** only after consumption of the ketone by its rapid hydrogenation. In AcOH, consumption of the keto form during the hydrogenation reaction is compensated by the fast re-equilibration of the hydrate to the ketone. Together with the intrinsically higher equilibrium amount of the keto form in AcOH, in this solvent the ketone concentration does not fall below a critical value, where hydrogenolysis of the hydrate becomes important. The competing reaction pathway and a drop of ee to 84% was only observed by addition of 0.5 ml water to the reaction mixture, corresponding to a water/**1** molar ratio of 15.

3.3. Selectivity enhancement by trifluoroacetic acid

The influence of a strong acid on the enantiodifferentiation has been investigated using trifluoroacetic acid (TFA) which is well miscible with organic solvents. The effect of TFA on the reaction rate and ee in THF and AcOH is shown in table 1. In both solvents TFA decreased the average rate by ~10% and improved the ee to 93%. The



Scheme 2. Equilibration of ethyl-4,4,4-trifluoroacetoacetate (**1**) in THF containing small amounts of water.

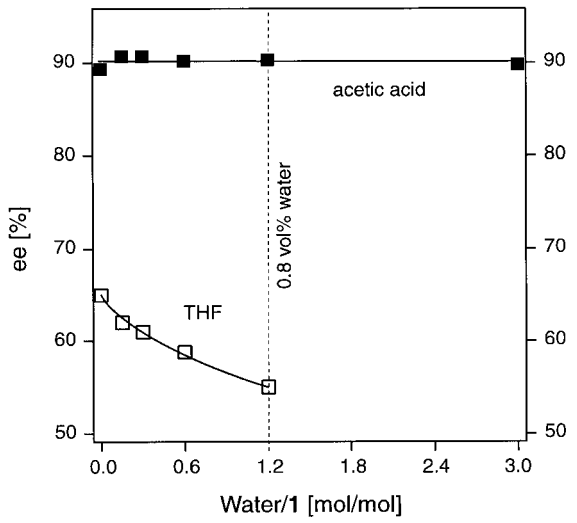


Figure 3. Effect of water addition on the enantioselectivity in AcOH and THF; standard conditions.

selectivity enhancement is particularly striking in THF. A further increase in ee to 96% could be achieved by using a mixture of AcOH and THF and lowering the temperature to 0 °C.

The efficiency of hydrogenation of the analogous methyl- (**4**) and isopropylester (**5**) was almost the same, affording 95 and 96% ee, respectively. This is interesting information for future mechanistic studies, indicating that in the enantio-differentiating step the size of the alkoxy group is not important.

Another interesting point is that small amounts of TFA, 0.8–2 vol% related to the solvent or 0.28–0.71 mol% related to **1**, was sufficient for the positive effect on ee. This is an indication that special interactions between TFA and the reactant and/or modifier are

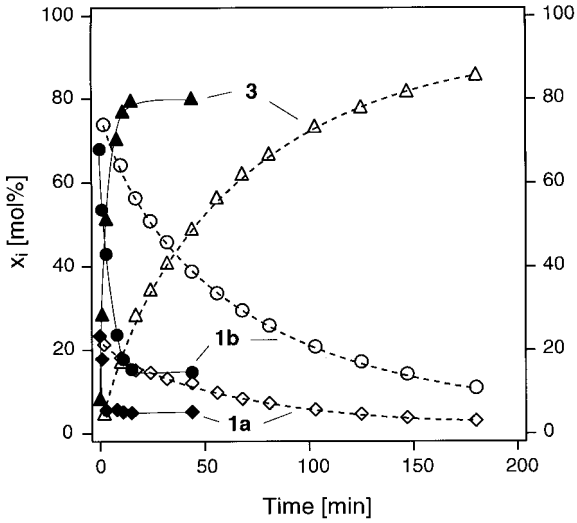


Figure 4. NMR measurement of hydrate (**3**) formation from **1** in THF and AcOH. Concentrations according to the standard reaction conditions, except that 0.8 vol% water was added at $t = 0$ (water/**1** = 1.2). Closed symbols: equilibration in AcOH; open symbols: equilibration in THF.

Table 1
Influence of acids on the hydrogenation of trifluoro-β-ketoesters **1**, **4** and **5**

Solvent	TFA (μl)	T (°C)	**1**		**4**		**5**	
			ee (%)	TOF (h^{-1})	ee (%)	TOF (h^{-1})	ee (%)	TOF (h^{-1})
THF	—	20	68	2120	—	—	—	—
AcOH	—	20	90	1660	90	1530	89	1410
THF	100	20	93	1850	92	1400	93	1610
AcOH	40	20	93	1530	—	—	—	—
THF/AcOH [a]	100	0	96	640	95	570	96	520

[a] 2.5 ml of each solvent.

responsible for the selectivity enhancement. Török *et al.* have shown recently that addition of TFA to acetic acid or toluene enhances the ee in ethyl pyruvate hydrogenation with the Pt-cinchonidine system but only under conditions far from the optimum [25].

4. Discussion

4.1. Solvent effect

In the hydrogenation of some activated ketones such as α-ketoesters [20,22], α-ketolactones [21], and pyrrolidine-triones [26] over cinchona-modified Pt, increasing solvent polarity diminishes the enantioselectivity. The only exceptions from this negative correlation are the ee's achieved in acidic solvents which are higher than expected from the solvent polarity. Another recent example of this type of solvent effect is the enantioselective hydrogenation of α,β-unsaturated carboxylic acids over CD-modified Pd. The alkenoic acid dimer–CD complex is stabilized best in cyclohexane affording much better ee's than in polar solvents [16,27]. Similar effects are generally observed when intermolecular complexes of the reacting compounds are favourable for the (stereochemical) outcome of the reaction. Strongly polar solvents disturb these interactions. Furthermore, it was shown that solvent polarity influences the conformation of CD and the most favourable conformation for α-ketoester hydrogenation (open (3)) is favoured in apolar and acidic solvents [28–30].

The clear positive correlation between solvent polarity and enantioselectivity in the hydrogenation of **1** indicates that the reactant–modifier interaction over cinchona-modified Pt is different from that proposed for α-ketoester hydrogenation [31].

When searching for a feasible explanation for the different impact of addition of water, we have to consider that solvent polarity has a strong influence on the keto-enol equilibrium of β-diketones [32]. Due to the higher polarity and the hydrogen bond donor ability of acetic acid, the keto-enol equilibrium of **1** is shifted towards the keto form **1a** when replacing THF by AcOH (table 2). In analogy, the ketone-hydrate equilibrium is shifted in favour of the ketone when changing from THF to AcOH, both solvents containing identical amounts of water. These two combined effects are responsible for the higher equilibrium amount of ketone **1a** in AcOH. In combination with the much faster equilibration in AcOH (figure 4), this is the reason for the suppression of hydrate hydrogenolysis up to relatively high water concentrations (figure 3). This effect is of great practical importance because it is difficult to completely remove water from AcOH. Still, even if the hydrate **3** is only a spectator species in AcOH, its presence cannot be neglected as it can interact with the modifier or other equilibrated species.

4.2. Role of strong acid

Our suggestion that the high ee obtained in AcOH is mainly due to its solvent properties and cannot simply be

Table 2
Equilibrium fraction of keto **1a**, enol **1b** and hydrate **3** species in THF and AcOH, with and without water, determined by NMR spectroscopy. Concentrations are set according to general reaction procedure

Solvent	Water addition (vol %)	Equilibrium time (h)	**1a** (%)	**1b** (%)	**3** (%)
THF	0	0	20.7	78.4	0.9
AcOH	0	0.5	23.4	68	8.4 [a]
THF	0.8	8	0.9	3.6	95.5
AcOH	0.8	0.5	5.2	14.6	80.0

[a] The deuterated acetic acid contained a small amount of water, leading to hydrate formation.

attributed to an H-bond interaction with (or protonation of) the modifier seemingly contradicts the beneficial effect of even small amounts of TFA (table 1). The remarkable improvement in ee in THF (and other non-acidic solvents) must be connected with the stronger acidity of TFA, as the changes in solvent properties by addition of 0.8 vol% TFA are expected to be minor. It has been shown [33] that small amounts of TFA ($pK_a = 0.2$) can protonate both the quinuclidine and the quinoline N atoms of the cinchona alkaloid, while the lower acidity of AcOH ($pK_a = 4.75$) is sufficient only to protonate the more basic quinuclidine N ($pK_a = 10.0$). Protonation of the weakly basic quinoline N ($pK_a = 5.8$) is expected to influence the adsorption strength and geometry of the modifier on the Pt surface and thus its interaction with the reactant.

5. Conclusions

A systematic investigation of the effects of solvents and acids on the hydrogenation of ethyl-4,4,4-trifluoroacetoacetate **1** contributed to a significant improvement in the enantioselectivity of the Pt–cinchona system. To our knowledge, the 93–96% ee and 640–1850 h^{-1} TOF represent the best values reported for the catalytic synthesis of the versatile chiral building block **2**. Similar high ee's were obtained for the methyl and isopropyl esters. No systematic optimization has yet been made. It is expected that particularly the reaction rate can be improved by increasing the hydrogen pressure or reactant concentration.

The studies revealed some crucial differences compared to the thoroughly investigated hydrogenation of α-ketoesters and other activated ketones on cinchona-modified Pt. The unusual effects of solvents and TFA seem to be a good starting point for further mechanistic investigations aiming at a deeper understanding of this synthetically important reaction.

References

[1] T. Sugimura, Catal. Surv. Jpn. 3 (1999) 37.
[2] T. Osawa, T. Harada and O. Takayasu, Top. Catal. 13 (2000) 155.
[3] A. Baiker and H.U. Blaser, in: *Handbook of Heterogeneous Catalysis*, Vol. 5, eds. G. Ertl, H. Knözinger and J. Weitkamp (VCH Publishers, Weinheim, 1997).
[4] P.B. Wells, K.E. Simons, J.A. Slipszenko, S.P. Griffiths and D.F. Ewing, J. Mol. Catal. A. 146 (1999) 159.
[5] G.J. Hutchings, Chem. Commun. (1999) 301.
[6] G.V. Smith and F. Notheisz, *Heterogeneous Catalysis in Organic Chemistry* (Academic Press, San Diego, 1999).
[7] T. MaIlat, M. Bodmer and A. Baiker, Catal. Lett. 44 (1997) 95.
[8] K. Balazsik, B. Török, K. Felföldi and M. Bartok, Ultrason. Sonochem. 5 (1999) 149.
[9] M. von Arx, T. Mallat and A. Baiker, J. Catal. 193 (2000) 161.
[10] D. Blanc, V. Ratovelomanana-Vidal, J.-P. Gillet and J.-P. Genet, J. Organomet. Chem. 603 (2000) 128.
[11] S.P. Götzö, D. Seebach and J.-J. Sanglier, Eur. J. Org. Chem. (1999) 2533.
[12] L. Antolini, A. Forni, P. Davoli, I. Moretti and F. Prati, Tetrahedron Asym. 9 (1998) 285.
[13] D. Seebach, P. Renaud, W.B. Schweizer and M.F. Züger, Helv. Chim. Acta 67 (1984) 1843.
[14] Y. Kuroki, Y. Sakamaki and K. Iseki, Org. Lett. 3 (2000) 457.
[15] Y. Kuroki, D. Asada and K. Iseki, Tetrahedron Lett. 41 (2000) 9853.
[16] K. Borszeky, T. Bürgi, Z. Zhaohui, T. Mallat and A. Baiker, J. Catal. 187 (1999) 160.
[17] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry* (VCH, Weinheim, 1988).
[18] M. von Arx, T. Mallat and A. Baiker, Angew. Chem. Int. Ed. 40 (2001) 2302.
[19] M. von Arx, T. Mallat and A. Baiker, J. Catal. 201 (2001) in press.
[20] H.U. Blaser, H.P. Jalett and J. Wiehl, J. Mol. Catal. 68 (1991) 215.
[21] M. Schürch, O. Schwalm, T. Mallat, J. Weber and A. Baiker, J. Catal. 169 (1997) 275.
[22] B. Minder, T. Mallat, P. Skrabal and A. Baiker, Catal. Lett. 29 (1994) 115.
[23] A. Baiker, J. Mol. Catal. A: Chem. 115 (1997) 473.
[24] F. Notheisz and M. Bartok, in: *Fine Chemicals through Heterogeneous Catalysis*, eds. R.A. Sheldon and H.v. Bekkum (Wiley-VCH, Weinheim, 2001).
[25] B. Török, K. Balázsik, K. Felföldi and M. Bartók, Stud. Surf. Sci. Catal. 130 (2000) 3381.
[26] A. Szabo, N. Künzle, T. Mallat and A. Baiker, Tetrahedron Asym. 10 (1999) 61.
[27] K. Borszeky, T. Mallat and A. Baiker, Catal. Lett. 41 (1996) 199.
[28] T. Bürgi and A. Baiker, J. Am. Chem. Soc. 120 (1998) 12920.
[29] G.D.H. Dijkstra, R.M. Kellogg, H. Wynberg, J.S. Svendsen, I. Marko and K.B. Sharpless, J. Am. Chem. Soc. 111 (1989) 8069.
[30] G.D.H. Dijkstra, R.M. Kellogg and H. Wynberg, J. Org. Chem. 55 (1990) 6121.
[31] A. Baiker, J. Mol. Catal. A. 163 (2000) 205.
[32] J. Emsley, in: *Structure and Bonding*, Vol. 57 (Springer-Verlag, Berlin, 1984).
[33] W.-R. Huek, T. Mallat and A. Baiker, J. Catal. 200 (2001) 171.