Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Molecular Catalysis A: Chemical 212 (2004) 205–209
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Rhodium-catalyzed heterogeneous enantioselective hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone

Reto Hess, Frank Krumeich, Tamas Mallat, Alfons Baiker*

Institute for Chemical and Bioengineering, Swiss Federal Institute of Technology, ETH-Hönggerberg, Wolfgang Pauli Strasse 10, CH-8093 Zurich, Switzerland

Received 21 August 2003; received in revised form 23 October 2003; accepted 23 October 2003

Abstract

Asymmetric hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone (**1**) to 1-[3,5-di-(trifluoromethyl)-phenyl]ethanol (**2**) was studied over 5 wt.% Rh/Al_2O_3 modified by cinchonidine (CD) and its *O*-methyl, *O*-ethyl, *O*-phenyl, *O*-trimethylsilyl, *N*-methyl, and *N*-benzyl derivatives. Replacement of CD by the ether derivatives resulted in the inversion of enantioselectivity from (*S*)-**2** to (*R*)-**2**, and an improvement in chemoselectivity up to 100%. Interestingly, *O*-phenyl-CD (36% enantiomeric excess (ee)) is a more effective chiral modifier for the reaction than CD (27% ee). CD and its ether derivatives induced a small rate acceleration compared to the unmodified reaction. The basic quinuclidine N of CD seems to be a necessary prerequisite for enantioselection, whereas the role of the OH group is not clear yet. Blocking of the OH group changes the absolute configuration of the major enantiomer.

Keywords: Asymmetic hydrogenation; 3,5-Di-(trifluoromethyl)-acetophenone; Rh/alumina; Cinchonidine derivatives; Inversion of enantioselectivity

1. Introduction

Despite of the intensive research in the field of heterogeneous enantioselective catalysis, only one approach, the use of metal hydrogenation catalysts modified by strongly adsorbing chiral organic molecules has yet afforded over 90% enantiomeric excess (ee) [1,2]. Effective catalysts are: (i) the Ni–tartaric acid system for the hydrogenation of β-functionalized and unfunctionalized aliphatic ketones [3–5]; (ii) the Pt–cinchona system for activated ketones [6–9]; and (iii) the Pd–cinchona system for α-functionalized olefins [10–12] and 2-pyrones [13].

While in homogeneous enantioselective hydrogenation low-valent Ru, Rh and Ir complexes stabilized by various chiral ligands are the most active and selective catalysts [14], these metals are characterized by moderate enantioselectivity in heterogeneous catalytic hydrogenations. Recently, cinchona-modified Rh has generated some interest in the hydrogenation of ethyl pyruvate [15–18]. Fine tuning of the reaction conditions and the catalyst composition (Rh nanoclusters supported on TS-1) resulted in 63% ee [19] – a value that is still far from the optimum reported for cinchona-modified Pt/Al_2O_3 (98%, [20]).

Here, we report the enantioselective hydrogenation of an aromatic ketone, 3,5-di-(trifluoromethyl)-acetophenone, over a 5 wt.% Rh/Al_2O_3 catalyst (Scheme 1). This reaction was moderately enantioselective with the Pt/Al_2O_3–cinchonidine system: only 46% ee was obtained at room temperature and 10 bar [21]. The aim of the present study was to clarify whether Rh, chirally modified by cinchonidine and some of its simple derivatives, would be an alternative for this reaction.

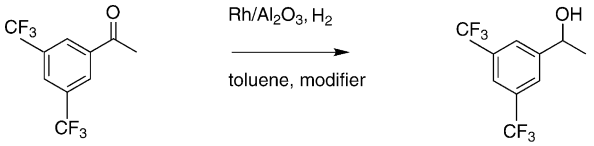
2. Experimental

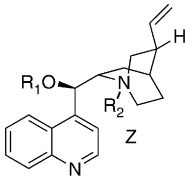
2.1. Materials

3,5-di-(trifluoromethyl)-acetophenone (**1**, ABCR), cinchonidine (CD, Fluka), *N*-benzylcinchonidinium chloride (*N*-BzCDCl, Fluka) and cinchonidine hydrochloride (CD·HCl, Sigma) were used as received. Ethoxycinchonidine (EtOCD), phenoxycinchonidine (PhOCD) and trimethylsiloxycinchonidine (TmsOCD) were supplied by Ubichem. Methoxycinchonidine (MeOCD) and *N*-methylcinchonidinium chloride (*N*-MeCDCl) were prepared

* Corresponding author. Tel.: +41-1-632-31-53; fax: +41-1-632-11-63.
E-mail address: baiker@tech.chem.ethz.ch (A. Baiker).

1381-1169/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2003.10.030





Modifier	R_1	R_2	Z
CD	H	-	-
MeOCD	methyl	-	-
EtOCD	ethyl	-	-
PhOCD	phenyl	-	-
TmsOCD	trimethylsilyl	-	-
CD•HCl	H	-	HCl
N-MeCDCl	H	methyl	Cl^-
N-BzCDCl	H	benzyl	Cl^-

Scheme 1. Hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone (**1**) to the corresponding alcohol over chirally modified Rh/Al_2O_3 and the structure of modifiers.

according to known methods [10]. Elementary analysis and NMR spectroscopic data were in good agreement with the structure of the modifiers. ^1H and ^{13}C NMR spectra were measured using a DPX 300 spectrometer.

2.2. Catalytic hydrogenation

According to the standard procedure, the 5 wt.% Rh/Al_2O_3 catalyst (Engelhard 8001 ESCAT 34) was pre-reduced before use in a fixed-bed reactor by flushing with N_2 at 400 °C for 30 min, followed by a reductive treatment in H_2 for 90 min at the same temperature. After cooling to room temperature in hydrogen, the catalyst was immediately transferred to the reactor. This procedure is the same as described for Pt/Al_2O_3 [22].

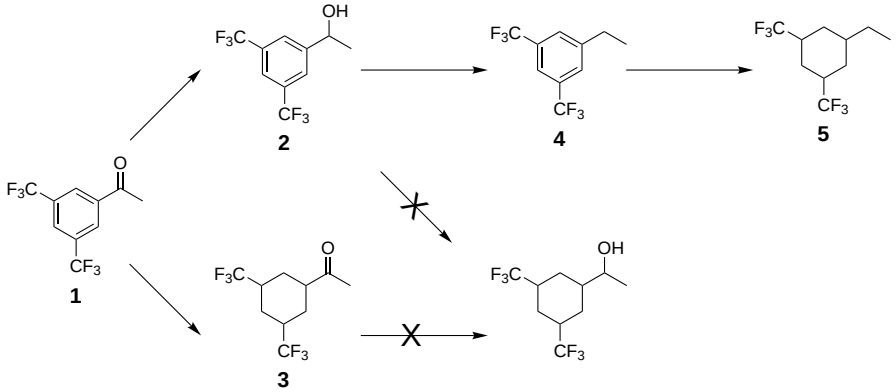
Hydrogenations were carried out in a parallel pressure reactor system Endeavor^{TM}, with eight mechanically stirred 15 ml stainless steel reactors equipped with glass liners. Control experiments using different amounts of catalyst and varying the stirring frequency (500–1000 rpm) did not indicate any mass transport limitation for the relatively slow reactions. Under standard conditions 42 ± 2 mg catalyst, 1.84 mmol substrate, 6.8 μmol modifier and 5 ml solvent were stirred (500 rpm) at 10 bar total pressure and room temperature (23–25 °C) for 2 h. Deviations from this procedure will be indicated in the text.

Conversion and ee were determined by an HP 6890 gas-chromatograph equipped with a chiral capillary column (WCOT fused silica 25 m × 0.25 mm, coating CP-Chirasil-Dex CB, Chrompack). Enantioselectivity is expressed as ee (%) $= 100 \times |(R - S)|/(R + S)$. The products were identified by GC–MS. Reproducibility of ee was within ±0.5%. The optical isomers were identified by comparison of their optical rotation (Perkin-Elmer 241 Polarimeter) with literature data [23,24].

2.3. TEM-measurements

For high resolution transmission electron microscopy (HRTEM), the material was dispersed in ethanol and

Table 1
Product distribution in the hydrogenation of 3,5-di-(trifluoromethyl)- acetophenone (**1**) over 5 wt.% Rh/Al_2O_3 under standard conditions, and the influence of CD derivatives on the rate and chemoselectivity



Modifier	Conversion (%)	Selectivity (%)			
		2	**3**	**4**	**5**
–	27	72	15	16	7
CD	30	93	4.5	1	1.5
MeOCD	43	94	3	1	2
EtOCD	40	96	2.5	0.5	1
PhOCD	36	97	2	0.5	0.5
TmsOCD	23	100	0	0	0
CD·HCl	20	91	6	1.5	1.5
N-MeCDCl	26	73	16	5	6
N-BzCDCl	20	90	6.5	1.5	2

deposited onto a perforated carbon foil supported on a copper grid. The investigations were performed on a Tecnai F30 microscope (Philips; field emission cathode, operated at 300 kV). Scanning transmission electron microscopy (STEM) images, obtained with a high-angle annular dark field (HAADF) detector, reveal the metal particles with bright contrast (Z contrast). Energy dispersive X-ray spectroscopic (EDS) analysis of the samples was facilitated by an EDAX system attached to the Tecnai F30 microscope.

3. Results and discussion

3.1. Chemoselectivity in the hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone

The Rh-catalyzed hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone (**1**, Table 1) was moderately selective in the absence of chiral modifier. Three byproducts could be detected, which were formed by C–O bond hydrogenolysis (**4** and **5**) and/or saturation of the aromatic ring (**3** and **5**).

CD and its ether derivatives improved the chemoselectivity to the desired aromatic alcohol 1-[3,5-di-(trifluoromethyl)-phenyl]ethanol (**2**). Interestingly, by increasing the size of the ether group the chemoselectivity to the main product increased up to 100% (TmsOCD). The chemoselectivity was lower again when replacing CD by its hydrochloride (CD·HCl) or by one of the quaternerized derivatives *N*-MeCDCl and *N*-BzCDCl. Thus, we attribute the improved chemoselectivity mainly to the effect of the basic quinuclidine N-atom of CD, though steric effects in the ether derivatives of CD are also important in the substrate–modifier interaction. Note that on Pt/Al_2O_3 the chemoselectivity to 3,5-di-(trifluoromethyl)-phenylethanol was always 99% or higher [8].

3.2. Role of catalyst pretreatment

Under standard conditions, the Rh/Al_2O_3 catalyst was pretreated at 400 °C in flowing hydrogen before hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone. A reductive treatment at elevated temperature was shown to increase considerably the enantioselectivity of the Pt-CD system in the hydrogenation of activated ketones [6,22]. The control experiments, however, revealed that this catalyst pretreatment is not necessary for Rh/Al_2O_3. Using the Rh/Al_2O_3-CD system under standard conditions, the ee increased only by 1% (from 26 to 27%) after the pretreatment. The effect of this reductive catalyst pretreatment on the reaction rate was bigger: the conversion after 2 h increased from 20 to 30%.

HRTEM measurements indicated that heat treatment in hydrogen did not change significantly the metal particle size but determination of the average metal particle size failed due to the presence of big agglomerates of irregular shape. The STEM images of the pretreated and untreated

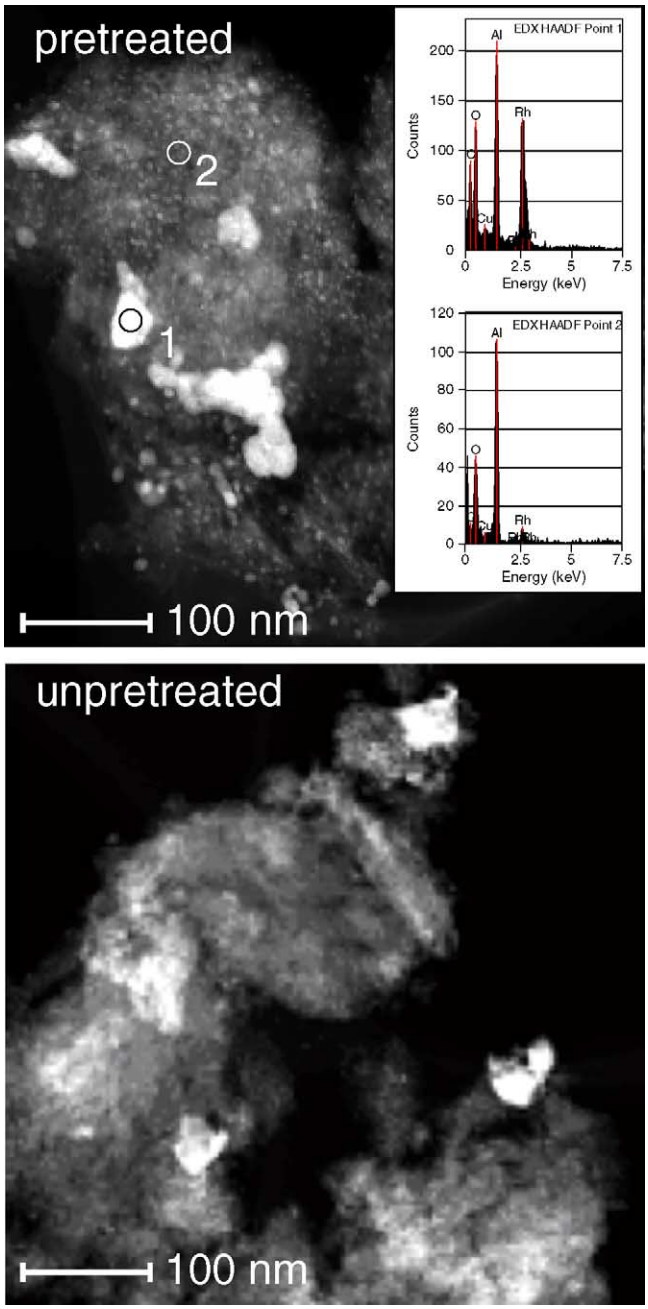


Fig. 1. Electron microscopic investigation of the 5 wt.% Rh/Al_2O_3 catalyst. Top: STEM image of the catalyst pretreated at 400 °C in hydrogen with EDS spectra obtained at circles 1 and 2. Bottom: STEM image of the unpretreated catalyst.

Rh/Al_2O_3 catalysts are presented in Fig. 1. EDX analysis confirmed that the huge bright structures are really agglomerated Rh particles. Since a decrease in average particle size during hydrogen treatment at elevated temperature is unlikely, the higher reactivity of the pretreated catalyst is attributed to removal of some surface impurities originating from the catalyst precursor and thus the increase of the number of active sites available for the reaction.

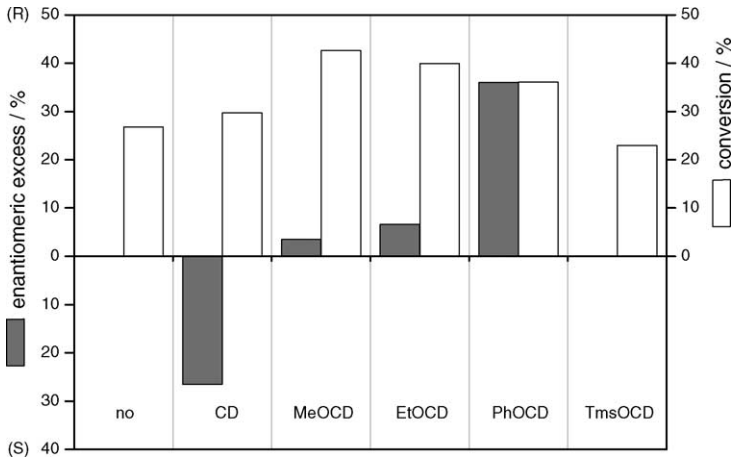


Fig. 2. Hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone (**1**) over 5 wt.% Rh/Al_2O_3 modified by CD and its ether derivatives (standard conditions, see experimental part).

3.3. Effect of pressure

The influence of pressure was investigated in the range 1–23 bar. With increasing pressure, the reaction time necessary to reach 25% conversion decreased by a factor of 6 under otherwise standard conditions. The ee remained almost constant over the whole pressure range (27% at 1 bar and 26% at 23 bar), indicating that the surface hydrogen concentration does not play a significant role in the enantioselection. For comparison, in the Rh-catalyzed enantioselective hydrogenation of ethyl pruvate the ee increased with increasing pressure but the reaction rate remained unaffected [19].

3.4. Hydrogenations with ether derivatives of cinchonidine

In order to clarify the role of the OH group of CD in the substrate-modifier interaction(s), various CD derivatives (Scheme 1) have been tested in the Rh-catalyzed hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone (**1**). The conversions and enantioselectivities are compared in Fig. 2. Replacement of CD by MeOCD, EtOCD or PhOCD inverted the enantioselectivity from an excess of (*S*)-**2** (27%) to (*R*)-**2**. With increasing bulkiness of the ether group the ee increased up to 36% for PhOCD. An exception was TmsOCD that did not generate any ee at all. In contrast, a strong interaction between **1** and TmsOCD is indicated by the complete suppression of hydrogenolysis and aromatic ring hydrogenation type side reactions, leading to a remarkable improvement of chemoselectivity from 72 to 100% (Table 1).

It is also seen from Fig. 2 that CD and its ether derivatives, except TmsOCD, induced some rate acceleration compared to the unmodified reaction. This rate acceleration, however, was always less than two-fold.

A comparison to chirally modified Pt/Al_2O_3 [21] reveals an astonishingly similar behavior concerning the rate acceleration induced by the cinchona-based modifiers, the formation of (*S*)-**2** in the presence of CD, the inversion of ee by replacing CD by its ether derivatives, and the zero ee obtained with TmsOCD.

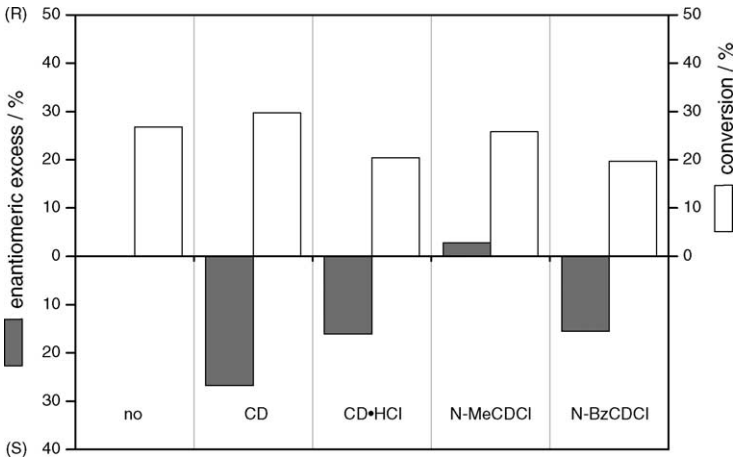


Fig. 3. Hydrogenation of 3,5-bis(trifluoromethyl)-acetophenone (**1**) over 5 wt.% Rh/Al_2O_3, modified by *N*-substituted cinchona alkaloids (standard conditions, see experimental part).

The conclusion that can be drawn from these experiments is that the OH group of CD plays a critical role in the enantioselection. Blocking of this functional group does not hinder the substrate–modifier interaction but changes the absolute configuration of the major enantiomer and this pathway is even faster.

3.5. Influence of protection of the quinuclidine N-atom of cinchonidine

Hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone (**1**) resulted in close to zero ee when the quinuclidine N-atom was methylated (*N*-MeCDCl, Fig. 3). Hydrogenation with the *N*-benzyl derivative (*N*-BzCDCl) afforded 15.5% ee that is attributed to hydrogenolysis of the C–N bond (debenzylation) and formation of CD·HCl, a moderately efficient modifier. The control experiment with CD·HCl gave about the same ee (16%) and conversion as *N*-BzCDCl. All reactions carried out in the presence of cinchonidinium chlorides were slower than the unmodified reaction.

These experiments indicate the fundamental role of the basic quinuclidine N-atom in the substrate-modifier interaction resulting in enantiodiscrimination. Effective blocking of this function in *N*-MeCDCl practically ceases the enantioselection. Note that this behavior is general for all hydrogenation reactions on cinchona-modified Pt [25,26] and Pd [10,27,28].

4. Conclusions

Hydrogenation of 3,5-di-(trifluoromethyl)-acetophenone (**1**) was studied over chirally modified 5 wt.% Rh/Al_2O_3 at room temperature and 10 bar. The best modifier, *O*-phenyl-cinchonidine, afforded 97% chemoselectivity and 36% ee to (*R*)-1-[3,5-di-(trifluoromethyl)-phenyl]ethanol (**2**), at 36% conversion in 2 h. This is the first example in heterogeneous asymmetric hydrogenations where a derivative of CD provides higher enantioselectivity than CD itself. For comparison, under the standard conditions applied here CD-modified 5 wt.% Pt/Al_2O_3 afforded 46% ee to (*S*)-**2** at 12% conversion of **1** [21].

Reactions carried out with CD derivatives protected at the OH or quinuclidine N functions may aid in exploring the role of these functions in the substrate–modifier interactions and provide a useful basis for future mechanistic studies.

Acknowledgements

Financial support by the Swiss National Science Foundation is kindly acknowledged. The authors also thank Argonaut Technologies for technical support for the parallel pressure reactor system.

References

[1] A. Baiker, Curr. Opin. Solid State Mater. Sci. 3 (1998) 86.
[2] M. Studer, H.U. Blaser, C. Exner, Adv. Synth. Catal. 345 (2003) 45.
[3] Y. Izumi, Adv. Catal. 32 (1983) 215.
[4] T. Osawa, T. Harada, O. Takayasu, Top. Catal. 13 (2000) 155.
[5] T. Sugimura, S. Nakagawa, A. Tai, Bull. Chem. Soc. Jpn. 75 (2002) 355.
[6] Y. Orito, S. Imai, S. Niwa, Nippon Kagaku Kaishi (1979) 1118.
[7] M. von Arx, T. Mallat, A. Baiker, Top. Catal. 19 (2002) 75.
[8] R. Hess, T. Mallat, A. Baiker, J. Catal. 218 (2003) 453.
[9] A. Baiker, J. Mol. Catal. A: Chem. 115 (1997) 473.
[10] K. Borszeky, T. Bürgi, Z. Zhaohui, T. Mallat, A. Baiker, J. Catal. 187 (1999) 160.
[11] Y. Nitta, Top. Catal. 13 (2000) 179.
[12] A. Tungler, G. Fogassy, J. Mol. Catal. A 173 (2001) 231.
[13] W.R. Huck, T. Mallat, A. Baiker, New J. Chem. 26 (2002) 6.
[14] R. Noyori, T. Ohkuma, Angew. Chem. -Int. Ed. 40 (2001) 40.
[15] H.U. Blaser, H.P. Jalett, D.M. Monti, J.F. Reber, J.T. Wehrli, Stud. Surf. Sci. Catal. 41 (1988) 153.
[16] W. Xiong, H.X. Ma, H. Chen, Y.Y. Huang, Y.L. Huang, X.J. Li, X.S. Li, J.Y. Qi, A.S.C. Chen, Chem. J. Chin. Univ. Chin. 23 (2002) 1758.
[17] Y. Huang, J. Chen, H. Chen, R. Li, Y. Li, L.-E. Min, X. Li, J. Mol. Catal. A: Chem. 170 (2001) 143.
[18] Y. Huang, Y. Li, J. Hu, P. Cheng, H. Chen, R. Li, X. Li, C.W. Yip, A.S.C. Chan, J. Mol. Catal. A: Chem. 189 (2002) 219.
[19] H.X. Ma, H. Chen, Q. Zhang, X.J. Li, J. Mol. Catal. A: Chem. 196 (2003) 131.
[20] B. Török, K. Balàzsik, M. Török, K. Felföldi, M. Bartók, Catal. Lett. 81 (2002) 55.
[21] R. Hess, A. Vargas, T. Bürgi, T. Mallat, A. Baiker, J. Catal., in press.
[22] M. Schürch, O. Schwalm, T. Mallat, J. Weber, A. Baiker, J. Catal. 169 (1997) 275.
[23] R.P. Singh, B. Twamley, L. Fabry-Asztalos, D.S. Matteson, J.M. Shreeve, J. Org. Chem. 65 (2000) 8123.
[24] A.D. Allen, V.M. Kanagasabapathy, T.T. Tidwell, J. Am. Chem. Soc. 107 (1985) 4513.
[25] H.U. Blaser, H.P. Jalett, Stud. Surf. Sci. Catal. 78 (1993) 139.
[26] A. Baiker, J. Mol. Catal. A: Chem. 163 (2000) 205.
[27] Y. Nitta, A. Shibata, Chem. Lett. (1998) 161.
[28] W.R. Huck, T. Bürgi, T. Mallat, A. Baiker, J. Catal. 200 (2001) 171.