

Homogeneous versus heterogeneous approach to the catalytic desymmetrisation of *meso*-anhydrides promoted by cinchona alkaloids

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Received 2 July 2001; accepted 24 September 2001

Abstract

The ring opening of the cyclic prochiral *cis*-1,2,3,6-tetrahydrophthalic anhydride **1** with methanol was investigated by using cinchona alkaloids such as quinine (QN) and quinidine (QD) as base catalysts. The effect of solvent, temperature, reaction time and catalyst amount on the yield and enantioselectivity was examined in the model reaction under homogeneous conditions. The best results (yields and ee values) were achieved by using QD as chiral catalyst. Moreover, as a hypothetical intermediate, an adduct between the anhydride and the catalyst which is responsible for both reagents activation and stereocontrol is proposed.

QD was then supported to both amorphous (KG-60) and mesoporous (MCM-41) siliceous materials through a thioether linker giving catalysts called KG-60-QD and MCM-41-QD, respectively. These materials were characterised by determining surface area, loading value and thermal stability. Comparison experiments showed that supported catalysts afforded product **3** in slightly lower yields and ee values with respect to the homogeneous counterpart. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Cinchona alkaloids; Asymmetric catalysis; *Meso*-anhydrides; Desymmetrisation; Heterogeneous catalysis

1. Introduction

Preparation of enantiopure products represents more and more an essential requirement in the synthesis of chiral fine chemicals, especially when these compounds find an application as building blocks in the synthesis of pharmaceuticals, cosmetics and agrochemicals [1].

Because of the high cost of chiral catalysts, their use on large and industrial scale is still restricted.

It is therefore very worthwhile to utilise supported chiral catalysts for asymmetric synthesis as these can then be easily recovered and recycled. Moreover, the anchoring of a homogeneous catalyst to the surface of an inorganic or organic polymer increases its life, allows an easy handling and separation from the reaction mixture, and minimises the waste production [2]. Unfortunately, the immobilised catalysts are often much less active than their homogeneous counterparts, due to diffusion limitations and to the steric congestion around the active sites.

The desymmetrisation of *meso*-compounds represents a very useful strategy in asymmetric synthesis, since it allows to control the generation of multiple

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stereocentres in a single step and, on the same time, enables the conversion of low value starting materials into more precious products.

In recent years different studies have been conducted on the ring opening of cyclic *meso*-anhydrides, promoted by commercially available alkaloids such as quinidine (QD) and quinine (QN) [3]. In particular, the reaction was claimed by Bolm to occur with high yields (94–98%) and good ee values (74–92%). However, the process is accompanied by some drawbacks, mainly due to the use of stoichiometric amounts of the promoter or the need for an additional base [4]. In the past, with the aim at employing a more easy-to-handle and reusable catalyst, polystyrene-supported QN was used but low stereoselectivity was observed [5].

In connection with our interest in the exploitation of supported organic catalysts [6,7], we undertook the study of the cinchona alkaloids-catalysed ring opening of *cis*-1,2,3,6-tetrahydrophthalic anhydride by methanol. The major goals of this study were: (i) to collect data concerning the possibility to run the homogeneous reaction under catalytic conditions with maximum ee, (ii) to support the chiral organic catalyst on different kinds of siliceous materials, and (iii) to compare the results of reactions carried out under homogeneous and heterogeneous conditions.

2. Experimental

2.1. Reagents and catalysts

All the reagents were used as-received without further purification. Solvents were distilled under nitrogen and dried before use. Before functionalisation, the siliceous supports were dried at 300 °C for 5 h and the final catalysts were dried at room temperature for 3 h under vacuum. The amorphous silica used was the commercial Kieselgel 60 (KG-60) purchased from Merck.

MCM-41 mesoporous material was prepared according to the procedure reported in the literature [8], by mixing, at room temperature and under vigorous stirring, commercial sodium silicate solution (Aldrich), 25% tetramethylammonium hydroxide solution, 25% cetyltrimethylammonium chloride solution and water, and ageing at 110 °C for 4 days the resulting gel (composition: SiO₂/0.39Na₂O/0.25CTMACl/

0.24TMAOH/50.7H₂O). The XRD pattern and the high surface area of the material are characteristic of MCM-41 silica with a long-range order in the mesopore arrangement.

2.1.1. Immobilisation of QD

Tethering of QD **4** on the siliceous support was performed following a modification of a procedure reported in the literature [9]. The selected siliceous support (KG-60 or MCM-41 silica) (5 g) was treated with 3-mercaptopropyl trimethoxysilane (45 mmol, 8.5 ml) in dry toluene (75 ml) at reflux for 24 h. After cooling, the mixture was filtered on Büchner funnel and the solid washed with Soxhlet apparatus for 16 h with a mixture of dichloromethane/diethyl ether at a ratio of 1/1. The obtained functionalised silica **8** was dried under vacuum for 3 h and refluxed, under nitrogen, in degassed chloroform (100 ml) for 48 h with QD **4** (15 mmol, 4.9 g) and α,α' -azoisobutyronitrile (α,α' -AIBN) (7.5 mmol, 1.2 g) as radical initiator. After filtration, the functionalised solid (KG-60-QD or MCM-41-QD) was washed with Soxhlet apparatus for 16 h with a mixture of dichloromethane/diethyl ether at a ratio of 1/1 and dried under vacuum at room temperature.

2.1.2. KG-60-QD capping

The capped KG-60-QD catalyst was obtained by reacting **8** with hexamethyldisilazane (HMDS) as reported in the literature [10].

2.2. Catalyst characterisation

XRD measurements of MCM-41 were carried out on a Philips PW 1480 diffractometer using monochromatised Cu K α radiation. Patterns were recorded over the range from 0 to 40° (2 θ) in steps of 0.02° with a contact time of 2 s at each point. The surface area was measured by BET method [11] using a Pulse-ChemiSorb 2705 Micromeritics instrument. Pore dimensions were determined by N₂ adsorption on a C. Micromeritics ASAP 2010 instrument. IR spectra were recorded on a Nicolet PC5 spectrophotometer preparing pellets of the siliceous materials. The pellets were dehydrated for 1 h at 70 °C before recording the spectra. Elemental analyses were performed on a Carlo Erba CHNS-O EA1108 Elemental Analyser. Thermogravimetric analyses were performed

on a Setaram TG-DTA 92 thermobalance in He/O₂ flow.

2.3. Reaction procedure

All reactions were carried out under nitrogen atmosphere in a Schlenk tube equipped with a magnetic stirrer. In a typical experiment, *cis*-1,2,3,6-tetrahydrophthalic anhydride **1** (0.5 mmol, 0.08 g) was dissolved in THF (6 ml) and cooled at -25°C under stirring. Then methanol (5 mmol, 0.2 ml) and the catalyst (0.05 mmol)¹ were added and the stirring was continued for 16 h at the same temperature. The solution obtained in the reactions performed under homogeneous catalysis was then extracted with 2 N HCl (2 × 5 ml) and the organic layer was dried over MgSO₄, whereas the slurry of the heterogeneous reactions was filtered on Büchner funnel and the catalyst washed with dichloromethane (10 ml). The final reaction mixture was then analysed by GC in a capillary Chrompack column (fused silica, 25 m × 0.25 mm, coating CP Chirasil-Dex CB) for the determination of ee and yield, using octadecane as internal standard.

2.4. Preparation of the QD derivatives

2.4.1. 9-O-Acetylquinidine (**6**)

QD (5 mmol, 1.6 g), acetic anhydride (5 ml) and the acidic zeolite HSZ-360² (0.1 g) were heated, under vigorous stirring, at 60°C for 2 h. After cooling, Et₂O (20 ml) was added to the mixture and the catalyst filtered off [12]. Removal of the solvent under reduced pressure and purification by flash chromatography through a silica gel column (using ethyl acetate/Et₃N 96:4 as eluent), afforded product **6** as a white solid in 82% yield: m.p. $98\text{--}99^{\circ}\text{C}$ (lit. m.p. $97\text{--}99^{\circ}\text{C}$ [13]).

2.4.2. 11-Propylthio-10,11-dihydroquinidine (**7**)

QD (5 mmol, 1.6 g), 1-propanethiol (40 mmol, 3.0 g, 3.6 ml) and α,α' -AIBN (1.25 mmol, 0.2 g) were

refluxed in degassed CHCl₃ (25 ml) for 48 h under nitrogen atmosphere. After cooling, the reaction mixture was extracted with 2 M HCl (2 × 20 ml). The aqueous extracts were washed with ether (2 × 20 ml) and made alkaline with 10% NaOH. The mixture was extracted with CH₂Cl₂ (3 × 20 ml) and the combined organic extracts were dried with MgSO₄. Evaporation of the solvent under reduced pressure and flash chromatography through a silica gel column (CHCl₃(70)–MeOH(20)–Et₃N(10) as eluent) afforded **7** as a white solid in 70% yield: m.p. $148\text{--}149^{\circ}\text{C}$; ¹H NMR (CDCl₃, 300 MHz): δ 8.71 (d, 1H, H-2, $J = 4.5$ Hz), 8.00 (d, 1H, H-3, $J = 9.2$ Hz), 7.53 (d, 1H, H-1, $J = 4.5$ Hz), 7.34 (dd, 1H, H-4, $J = 9.2$ and 2.7 Hz), 7.20 (d, 1H, H-5, $J = 2.7$ Hz), 5.60 (d, 1H, CHOH, $J = 4.2$ Hz), 3.89 (s, 3H, OCH₃), 3.1–2.7 (m, 5H, NCH and 2NCH₂), 2.49 (t, 2H, SCH₂, $J = 7.2$ Hz), 2.47 (t, 2H, CH₂S, $J = 7.1$ Hz), 1.95 (m, 1H, CHCH₂CH₂S), 1.8–1.1 (m, 10H, 6H-quinucl. and CH₃CH₂CH₂SCH₂CH₂), 1.00 (t, 3H, CH₃, $J = 7.4$ Hz) ppm; MS (CI): m/z (%) 401 (M⁺+1, 72), 400 (M⁺, 100), 357 (14), 324 (64), 212 (17); FT-IR: ν (KBr) 2935, 1622, 1512, 1262 cm⁻¹.

3. Results and discussion

3.1. Homogeneous reactions—optimisation of the process

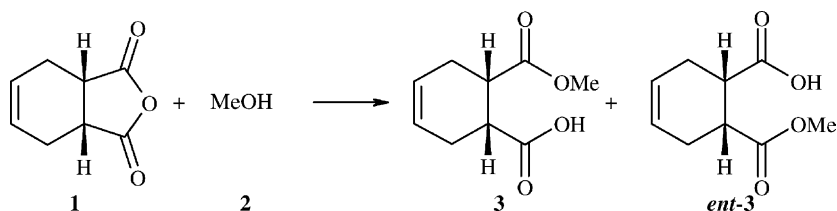
In a first series of experiments, the reaction between *cis*-1,2,3,6-tetrahydrophthalic anhydride **1** and methanol **2** (Scheme 1) was studied in the presence of a catalytic amount (10%) of QD **4** under homogeneous conditions. To optimise the experimental conditions, the influence of solvent, temperature, catalyst amount, reaction time and addition of base on the efficiency of the process was investigated, with particular regard to the enantioselectivity.

The reactions were performed at -25°C for 16 h because higher temperatures resulted in a decrease in ee value and at lower temperature the reaction rate became very low. Therefore, a further rate decrease should be expected under heterogeneous catalysis.

As can be seen from Table 1, the best ee values were obtained by carrying out the reaction in aprotic solvents of higher polarity (E_{T}^{N} value) [14]: THF was found to be the best solvent, while the use of methanol

¹ Under heterogeneous conditions, the catalyst amount used was determined on the basis of the QD loading value: KG-60-QD = 0.178 g and MCM-41-QD = 0.102 g.

² Zeolite HSZ-360 is a commercial (Tosoh Corp.) acid faujasitic-type catalyst with 13.9 SiO₂/Al₂O₃ molar ratio, pore size 7.4 Å, surface area 500 ± 10 m²/g, acidity 0.51 meq. H⁺/g and with the following chemical composition (wt.% dry basis): SiO₂ 89.0, Al₂O₃ 10.9, Na₂O 0.06.



Scheme 1. Reaction scheme.

Table 1
Solvent effect in the desymmetrisation reaction of **1** with methanol

Entry	Solvent	E_T^N	Yield (%)	ee (%)
a	Toluene	0.099	68	64
b	Diethylether	0.117	44	75
c	<i>tert</i> -Butylmethylether	0.148	61	80
d	THF	0.207	45	85
e	Methanol	0.608	98	24

as solvent–reagent led to an increase in the yield, but also to a considerable drop in stereocontrol.

Results from Table 2 show that the use of a catalytic amount of QD (**4/1** molar ratio: 0.1) allows to produce compound **3** with lower yield but with an ee value comparable with that of the stoichiometric reaction.

To improve the yield of the catalytic reaction, the effect of time was considered; we found that the yield raised the upper value of 96% after 36 h while preserving the same high ee (85%). These results are surprising since until now stoichiometric or in general large amounts of QD with respect to the reacting anhydride were utilised to achieve good ee values (95% ee by carrying out the reaction in toluene/ CCl_4 mixture at a ratio of 1:1 at -55°C [4]).

Finally, concerning the base addition effect, the reaction is faster in the presence of a stoichiometric amount of ethyl diisopropylamine, but the ee values

Table 2
Effect of QD amount in the desymmetrisation reaction of **1** with methanol

Entry	4/1 (mmol)	Yield (%)	ee (%)
a	0.05	21	70
b	0.1	45	85
c	0.2	50	85
d	1	89	86

Table 3
Efficiency of different cinchona-based catalysts on the desymmetrisation reaction of **1** with methanol

Entry	Catalyst	Yield (%)	ee (%)	Major product
a	QD 4	45	85	3
b	QN 5	37	65	ent-3
c	Derivative 6	28	56	3
d	Derivative 7	49	80	3

are lower (43%); further experiments carried out under the same conditions showed that the ethyl diisopropylamine itself promotes the process in 90% yield. On the basis of these results, operating at -25°C the presence of the amine additive is detrimental for the asymmetric induction.

Diastereomeric QN **5** (Fig. 1), which can be considered as pseudo-enantiomer of QD, afforded the ring opening product **ent-3** in a slightly lower enantiopurity (65%) (Table 3, entries a and b).

From our preliminary studies, it seems that the reaction could proceed through the formation of an adduct between the QD and the anhydride. In fact, mass analysis of an equimolecular solution of QD **4** and anhydride **1** in chloroform revealed the formation of a new species showing the m/z value corresponding to the sum of the two molecular weights, whose hypothetical structure is depicted in Fig. 2.

3.2. Heterogeneous reactions—optimisation of the process

The further goal was the heterogenisation of the organic catalyst by tethering the QD to the surface of a siliceous support. Two functional groups of compound **4** could be useful to this end: the carbon–carbon double bond and the hydroxy group. At first we prepared

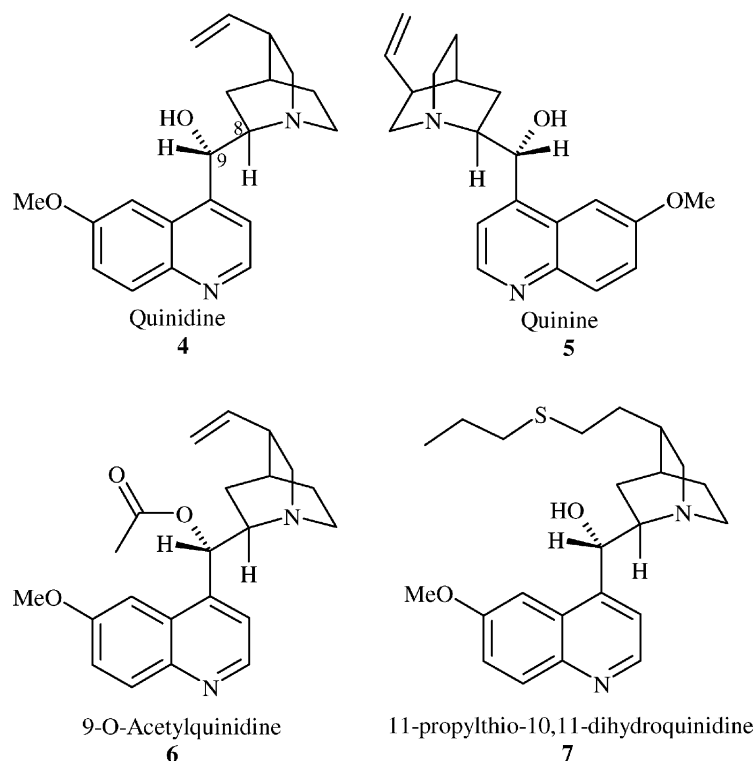


Fig. 1. Cinchona-based catalysts studied.

derivatives **6** and **7** (Fig. 1) by using modifications of conventional methods [5,12], with the aim of studying their activity and efficiency in the model reaction. From results of Table 3 (entries c and d), it appears that the best ee value is obtained with derivative **7**, suggesting a possible synergistic effect of the hydroxy and the tertiary nitrogen groups in the stereocontrol. Therefore, QD was anchored to the support through a thioether linker involving the C–C double bond

of **4** and the propanethiol moiety of the modified siliceous support **8** (Scheme 2). Two different inorganic supports were utilised: commercially available amorphous silica KG-60, showing a pore distribution ranging from micro- to macropores, and mesoporous silicas MCM-41, the structure of which contains a hexagonal array of mono-dimensional channels ($\varnothing = 38 \text{ \AA}$). Both the heterogeneous catalysts (KG-60-QD and MCM-41-QD) were characterised by elemental analysis, surface area and FT-IR spectroscopy which confirmed the successful tethering of the catalyst. These catalysts, as deduced from thermogravimetric analysis, are stable up to 150°C .

Next the solid catalysts (10 mol% of supported QD) were tested in the model reaction showing slightly different activity (Table 4). Although the ee values obtained under homogeneous conditions are better than those observed under heterogeneous conditions, the results obtained with KG-60-QD were good.

The yield of the reaction was next studied as function of time. As expected, the production of **3** during

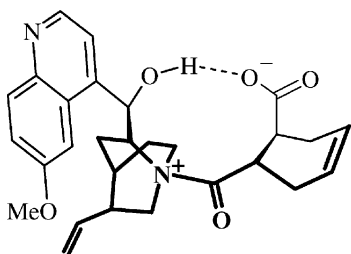
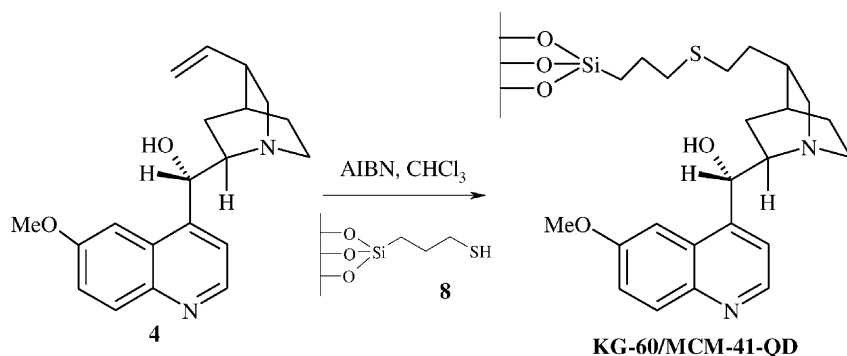


Fig. 2. Hypothesised active intermediate.



Scheme 2. Preparation of silica-supported QD.

Table 4

Efficiency of homogeneous and heterogeneous cinchona-based catalysts on the desymmetrisation reaction of **1** with methanol

Entry	Catalyst	Loading (mmol/g)	Surface area (m ² /g)	Yield (%)	ee (%)
a	QD 4	–	–	45	85
b	KG-60-QD	0.28	299	34	65
c	MCM-41-QD	0.49	685	30	65
d	Capped KG-60-QD	0.19	242	15	52

the time with the best supported catalyst (KG-60-QD) is lower than that promoted by the homogeneous counterpart (Fig. 3), due to the restricted diffusion of reactants and products in the heterogeneous material.

FT-IR spectra of KG-60-QD before (b) and after (c) the reaction together with that of the QD itself (a) are reported in Fig. 4. Spectrum (b), of freshly prepared catalyst, shows the characteristic bands of QD (1620, 1589 and 1509 cm⁻¹). A comparison of spec-

trum (b) with that of the reused KG-60-QD (spectrum (c)) shows that the catalyst is not damaged during the reaction.

To enlighten the possible role of the surface silanols, we carried out the model reaction by using the KG-60-QD capped with HMDS obtaining product **3** in 15% yield and 52% ee. This result could be explained taking into account a possible activation of reactants by surface silanols through H bond; of course

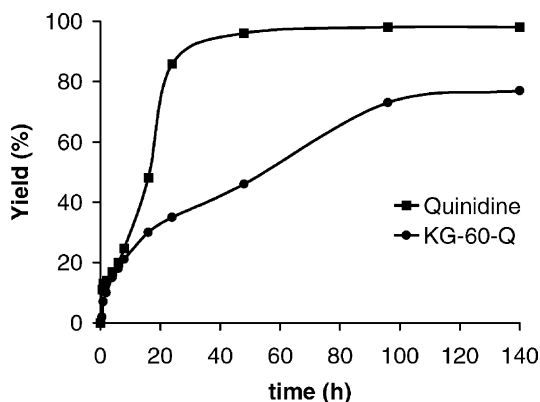
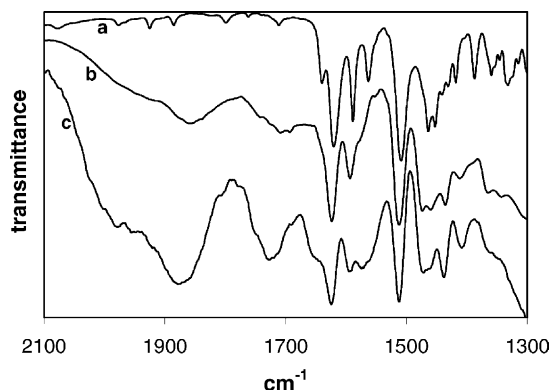
Fig. 3. Yield of product **3** as function of time in both homogeneous (■) and heterogeneous (●) reactions.

Fig. 4. Infrared spectra of QD (a), freshly prepared KG-60-QD (b), and reused KG-60-QD (c).

the capping of silanols with the bulky trimethylsilyl groups could hamper the interaction of the reactants with the active catalytic sites.

Finally, we faced the problem of the catalyst recycling. To this end KG-60-QD was filtered on Büchner funnel, washed with THF, dried under vacuum and reused. The catalyst could be utilised with similar results for at least three further cycles (yield, % (ee, %): first 32 (60), second 30 (59) and third 31 (61)).

4. Conclusions

Summarising, we have shown that the desymmetrisation of *cis*-1,2,3,6-tetrahydrophthalic anhydride **1** with methanol could be performed with high ee under homogeneous conditions using catalytic amounts of **4** and without need of additional bases. Moreover, we have proven that QD supported on commercially available silica KG-60 can be utilised as heterogeneous and reusable catalyst showing only little lower values of yield and ee with respect to the homogeneous counterpart.

Studies aimed at clarifying the formation of the adduct depicted in Fig. 2 and at extending the applicability of this methodology at different anhydrides are in progress.

Acknowledgements

Thanks are due to the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST),

Italy, the Consiglio Nazionale delle Ricerche (CNR), Italy, and the University of Bologna (National Project "Stereoselezione in Sintesi Organica"), for financial support. The authors are grateful to the Centro Interdipartimentale Misure (CIM) for the use of NMR and mass instruments, and to Mr. Pier Antonio Bonaldi (Lillo) for technical collaboration.

References

- [1] H.U. Blaser, *Tetrahedron* 2 (1991) 843.
- [2] R.A. Sheldon, *Chem. Ind. (London)* (1997) 12.
- [3] C. Bolm, A. Gerlach, C.L. Dinter, *Synlett* (1999) 195.
- [4] C. Bolm, I. Schiffrers, C.L. Dinter, A. Gerlach, *J. Org. Chem.* 65 (2000) 6984.
- [5] M. Inagaki, J. Hiratake, Y. Yamamoto, J. Oda, *Bull. Chem. Soc. Jpn.* 60 (1987) 4121.
- [6] G. Demicheli, R. Maggi, A. Mazzacani, P. Righi, G. Sartori, F. Bigi, *Tetrahedron Lett.* 42 (2001) 2401.
- [7] S. Carloni, D.E. De Vos, P.A. Jacobs, R. Maggi, G. Sartori, R. Sartorio, *J. Catal.*, in press.
- [8] R. Ryoo, J.M. Kim, *J. Chem. Soc., Chem. Commun.* (1995) 711.
- [9] C.E. Song, J.W. Yang, H.J. Ha, *Tetrahedron* 8 (1997) 841.
- [10] A. Cauvel, G. Renard, D. Brunel, *J. Org. Chem.* 62 (1997) 749.
- [11] S. Braunauer, P.H. Emmet, E. Teller, *J. Am. Chem. Soc.* 60 (1938) 309.
- [12] R. Ballini, G. Bosica, S. Carloni, L. Ciaralli, R. Maggi, G. Sartori, *Tetrahedron Lett.* 39 (1998) 6049.
- [13] H. Pracejus, *Justus Liebigs Ann. Chem.* 634 (1960) 9.
- [14] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, 1988.