Cascade approach for synthesis of *R*-1-phenyl ethyl acetate from acetophenone: Effect of support

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Abstract

One-pot synthesis of *R*-1-phenylethyl acetate starting from acetophenone hydrogenation was studied over supported palladium catalysts in combination with an immobilized lipase. Ethyl acetate was used as an acyl donor and the experiments were carried out under 1 bar hydrogen at 70 °C. In this work, the effect of support acidity was systematically investigated by using two mesoporous Pd–H–MCM-41 and Pd–Si–MCM-41 catalysts as hydrogenation catalysts. Furthermore their performance was compared with the performances of Pd–SiO$_2$ and Pd–Al$_2$O$_3$. The catalysts acidity was determined by pyridine adsorption while the metal crystallite sizes were measured by XRD technique. The initial hydrogenation rates of acetophenone decreased with increasing Pd crystallite sizes. Initially both *R*- and *S*-1-phenylethanol were formed with the same rates. After prolonged reaction times activities of both hydrogenation catalyst and lipase declined. The former catalyst deactivated due to formation of acetic acid via deacylation reaction, whereas ethanol formed as a stoichiometric product in acylation decreased the lipase activity. The formation of ethylbenzene via dehydration of an intermediate alcohol, (*R,S*)-1-phenylethanol was enhanced by acidic catalysts. The most selective catalyst for one-pot synthesis of *R*-1-phenylethylacetate was a slightly acidic Pd–Al$_2$O$_3$ in combination with lipase. A reaction network was proposed based on the kinetic data.
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1. Introduction

Cascade catalysis is a very intensively studied research area, being of great interest both in academia and in industry [1]. The idea is to perform several reactions in one reactor pot, thus saving equipment and separation costs in producing fine chemicals. One interesting model reaction is selective hydrogenation of acetophenone to racemic alcohol (*R,S*)-1-phenylethanol. The formed *R*-1-phenylethanol can be acylated with very high enantiomeric excess over enzymes, like lipase to produce chiral esters [2]. One of the simplest ester molecules is *R*-1-phenyl ethylacetate, which can be very selectively acylated over lipases according to Kazlauskas rule [3], since there exists a large phenyl group and a medium sized substituent, a hydroxyl group. Typically vinyl acetate has been used as an acyl donor and the

reaction proceeds relatively fast [2]. If the idea is to start from acetophenone hydrogenation in one-pot, vinyl acetate is not suitable acyl donor in the second step, since it is hydrogenated instantaneously. Acylation proceeds slightly slower with ethyl acetate, but since it is also suitable as solvent in the hydrogenation step [2], it has been used in the current work. Thus, the idea in the present work is to hydrogenate acetophenone selectively to (*R,S*)-1-phenylethanol with molecular hydrogen over a heterogeneous catalyst and to acylate with the enzyme the formed *R*-1-phenylethanol to the corresponding ester, namely *R*-1-phenyl ethyl acetate. According to our knowledge this concept has not been investigated before. On the other hand, a continuous hydrogenation–acylation was demonstrated in two consecutive reactors [4] or by using molecular hydrogen and a homogeneous metal complex as a hydrogenation and racemization catalyst, respectively [2].

Selective hydrogenation of acetophenone is the first step to proceed in one-pot synthesis of *R*-1-phenylethyl acetate. The hydrogenation reaction gives as products a racemic mixture of

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(*R,S*)-1-phenylethanol. Pd supported catalysts have been very selective to keep the phenyl ring intact in the hydrogenation of acetophenone [5], whereas over Pt catalyst also cyclohexyl products have been formed [6]. One potential side reaction using Pd supported catalysts, is however, hydrogenolysis of (*R,S*)-1-phenylethanol [5], which can be suppressed by adding bases into the reaction mixture or washing the catalysts with sodium hydroxide. Hydrogenolysis of (*R,S*)-1-phenylethanol is according to literature [7] catalyzed both by Brønsted and Lewis acid sites.

In the second step, the *R*-enantiomer is acylated to *R*-1-phenylethyl acetate. The *S*-enantiomer is not reacting over lipases [8]. Racemization of *S*-enantiomer has been performed over zeolites [9,10] or by using homogeneous complexes [2]. Zeolites are not suitable to use as racemization catalysts for *S*-1-phenylethanol in this work, since they promote acid catalyzed dehydration of (*R,S*)-1-phenylethanol to styrene [5]. There might be, however, other possibilities to racemize *S*-1-phenylethanol, by applying for instance vanadyl sulfate [11] and Ru-hydroxyapatite [12], which are not very acidic and thus in the presence of Pd and hydrogen do not catalyze dehydration of (*R,S*)-1-phenylethanol.

The aim in this paper was to study four different hydrogenation catalysts in one-pot synthesis of *R*-1-phenylethyl acetate, namely Pd–Al$_2$O$_3$, Pd–SiO$_2$ as well as two mesoporous catalysts being an acidic Pd–H–MCM-41 and a non-acidic Pd–Si–MCM-41. The correlation between the support acidity and the catalytic performance was established. Based on the kinetic data the reaction network was proposed.

2. Experimental

2.1. Catalyst synthesis

Five weight percent Pd–Al$_2$O$_3$ (UOP) and 5 wt.% Pd–SiO$_2$ (Merck) catalysts were prepared by vacuum evaporation impregnation method in a rotary evaporator using an aqueous solution of palladium nitrate (Degussa) as a precursor. The catalysts were dried at 110 °C and calcined in a muffle oven.

Synthesis of the Na/MCM-41 mesoporous molecular sieve was carried out in 300 ml autoclave using a method described in Refs. [13–15] with the following chemicals: fumed silica (Aldrich), tetramethylammonium silicate (TMSiO$_2$, Aldrich), sodium silicate (Na$_2$SiO$_3$), Merck), tetradecyl trimethyl ammonium bromide (CH$_3$(CH$_2$)$_{13}$N(CH$_3$)$_3$Br) Aldrich) and aluminium isopropoxide ([CH$_3$)$_2$CHO]$_3$Al), Aldrich) as aluminium source. The Si/Al ratio was 20 for Na–H–MCM-41. The synthesis was carried out at 100 °C. After filtering the synthesized mesoporous material Na/MCM-41 was dried at 110 °C and calcined at 530 °C. Ion-exchange of Na–MCM-41 was carried out with 1 M NH$_4$Cl for 24 h followed by washing with distilled water, drying at 110 °C and calcination at 450 °C for 4 h.

Synthesis of the Si–MCM-41 mesoporous molecular sieve was carried out in a 300 ml autoclave. The synthesis was performed by preparing solutions named here as A, B and C.

Solution A was prepared by mixing fumed silica (Aldrich) with distilled water under continuous stirring. Solution B was prepared by adding tetramethylammonium silicate (Sachem) to sodium silicate (Merck) and stirring for 15 min. Solution C was prepared by dissolving tetradecyl trimethyl ammonium bromide (Aldrich) in distilled water. Solution B was added to solution A slowly and stirred for 20 min, subsequently solution C was introduced under vigorous stirring. After measuring pH of the prepared gel it was introduced in a teflon cup, which was then inserted in an autoclave. The synthesis was performed at 100 °C in an oven. After completion of the synthesis, the reactor was quenched and the mesoporous material was filtered and washed thoroughly with distilled water. Synthesized Si–MCM-41 was dried at 110 °C and calcined at 550 °C. 5 wt% Pd loaded Pd–Si–MCM-41 and Pd–H–MCM-41 catalysts were prepared by vacuum evaporation impregnation method in a rotator evaporator (Buchi) using aqueous solution of palladium nitrate as precursor for palladium. The catalysts were dried at 110 °C and calcined at 400 °C in a muffle oven.

2.2. Catalyst characterization

The specific surface area was measured by nitrogen adsorption using Carlo Erba 1900 Instrument. The catalysts were out gassed at 150 °C for 3 h prior to the surface area measurements. The surface areas of catalysts were calculated with BET equation.

X-Ray powder diffraction was used for characterization of the mesoporous phase and measuring the Pd crystallite size with Philips PW1820 diffractometer using nickel filtered Cu K$_\alpha$ ($\lambda = 1.542$ Å) radiation operated at 40 kV/50 mA. The divergence of the primary X-ray beam was limited by an automatic divergence slit (ADS) and a 15 mm mask. The irradiated sample length was set at a fixed 12 mm. On the diffracted side there was a 0.2 mm receiving slit and a 1° anti-scatter slit. The measured diffractograms were analyzed using X'Pert HighScore software (Philips, 2001) and the Powder Diffraction File (PDF) database (PDF-2 sets 1–46, ICDD, 1996).

Temperature programmed desorption techniques was used to study the amount of hydrogen desorbed from some catalysts. The heating was performed under helium flow up to 700 °C for 60 min with the temperature ramp 10 °C per min (Micromeritics, Autochem 2910). The catalysts were reduced at 100 °C for 30 min under hydrogen, thereafter they were cooled down to the ambient temperature.

Scanning electron microscopy pictures were taken with 360 LEO Electron Microscopy LTD equipped with a secondary and backscattered electron detector from Na–MCM-41 for revealing the particle morphology.

The acidity of Al$_2$O$_3$ (UOP) and H–MCM-41 was studied by pyridine adsorption using infrared spectroscopy (ATI Mattson FTIR). Thin wafers (10–12 mg/cm^2) were prepared from support materials. The pyridine (>99.5%, a.r.) was adsorbed at 100 °C for 30 min and desorbed at 200 °C. The spectra were recorded at 100 °C with a spectral resolution of 2 cm^{-1}. Molar extinction coefficient for pyridine was determined by [16].

Table 1
Catalyst characterization results

Catalyst	BET specific surface area (m^2/g_{cat}).	Concentration of Brønsted acid sites ($\mu mol/g_{support}$)	Concentration of Lewis acid sites ($\mu mol/g_{support}$)	Average Pd crystallite size with XRD (nm)
Pd–H–MCM-41	902	89	168	3.9
Pd–Al$_2$O$_3$	306	7	156	7.1
Pd–Si–MCM-41	379	0	0	7.3
Pd–SiO$_2$	351	0	0	n.m.

n.m.: not measured.

2.3. Experimental setup

Experiments were performed in a glass reactor under atmospheric hydrogen (AGA 99.999) with 295 ml/min volumetric flow rate at 70 °C. The stirring speed was 370 rpm. Ethyl acetate (Fluka, >99%) was used as a solvent and as an acyl donor. The initial acetophenone concentration was 0.02 mol/l. The liquid phase volume was 250 ml. The masses of both hydrogenation catalyst and the immobilized enzyme catalysts (Novozym 435) were 125 mg, if other amounts were not specified. The hydrogenation catalyst was pre-reduced with flowing hydrogen at 100 °C for 30 min prior injection of the lipase, the reactant and the solvent.

2.4. Product analysis

The products were analyzed by a gas chromatograph equipped with a chiral column (CP Chirasil Dex (250 μm × 250 μm × 25 m) and a flame ionization detector. The samples were analyzed by using the following temperature programme 100 °C (1 min)–0.30 °C/min – 130 °C – 15 °C/min – 200 °C (10 min). The temperature of the injector and the split ratio were 280 °C and 100:1, respectively. The GC-method was calibrated with the following chemicals: (*R*)-1-phenyl ethanol ((*R*)-1-PE) (Sigma), (*R*,*S*)-1-phenyl ethanol (Fluka ≥ 98%) and ethyl benzene (Fluka, >99%). The products were identified with GC–MS. In some cases the water content in the reaction mixture was measured with Karl Fischer titration by Hydranal (Riedel de Häen, Composite 5).

3. Results and discussion

3.1. Catalyst characterization results

The specific surface areas of the four catalysts are given in Table 1. The largest BET specific surface area was obtained for Pd–H–MCM-41, whereas all the other three catalysts exhibited the BET surface areas in a range of 306–379 m^2/g_{cat}.

The existence of mesoporous phase of H–MCM-41 was revealed by the following characteristic peaks of MCM-41, namely the main peak at 2.56°, the second peak at 4.41°, third peak at 5.04° and the fourth peak at 7.1°. In Si–MCM-41 the corresponding peaks were observed at 2.52°, 4.39° and 5.04°. The fourth characteristic peak could not be discerned in Si–MCM-41.

The metal particle sizes were determined by XRD for Pd–Al$_2$O$_3$ and for Pd–H–MCM-41 (Table 1, Fig. 1a). For Pd–H–MCM-41 catalyst reduced at 100 °C for 30 min the fol-

lowing Pd peaks were found: Pd(1 1 1), at 2(39.962 °C, peak Pd(2 0 0) at 47.208 °C, peak Pd(2 2 0) at 68.083 °C and Pd(3 1 1) at 81.960 °C at 81.960. An average Pd crystallite size for this catalyst was 3.9 nm. Analogously for Si–MCM-41 the average Pd crystallite size was determined from XRD (Fig. 1b) being 7.3 nm. The same phases were observed for Pd–Si–MCM-41 as for Pd–H–MCM-41, but the angles were slightly shifted to larger levels for the former catalyst. For reduced Pd–Al$_2$O$_3$ catalyst only three forms of Pd were observed namely Pd(1 1 1), 40.086°2(, Pd(2 0 0), 46.148°2(and Pd(3 1 1), 82.173°2(giving an average Pd crystallite size of 7.1 nm. Pd particles were smaller in the mesoporous Pd–H–MCM-41 exhibiting both a higher concentration of Brønsted acid sites as well as 2.9-fold larger BET surface area than that of Pd–Al$_2$O$_3$. This result indicated that the larger BET surface area and the higher concentration of Brønsted acid sites facilitated the preparation of more dispersed Pd particles over H–MCM-41 than over Pd–Al$_2$O$_3$ since
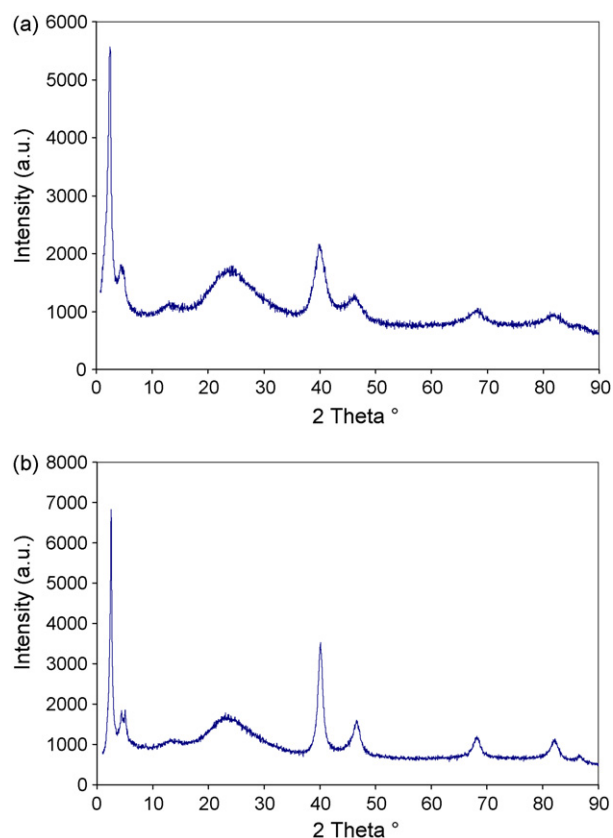

Fig. 1. The XRD pattern of the reduced (a) Pd–H–MCM-41 and (b) Pd–Si–MCM-41. Reduction procedure: 100 °C for 30 min.

Table 2
H$_2$ TPD results for Pd–Al$_2$O$_3$ and for Pd–SiO$_2$

Catalyst	Total amount of hydrogen desorbed (mmol/g$_{cat.}$)	T_{max} (°C)
Pd–Al$_2$O$_3$	0.0067	307, 367
Pd–SiO$_2$	0.002	364

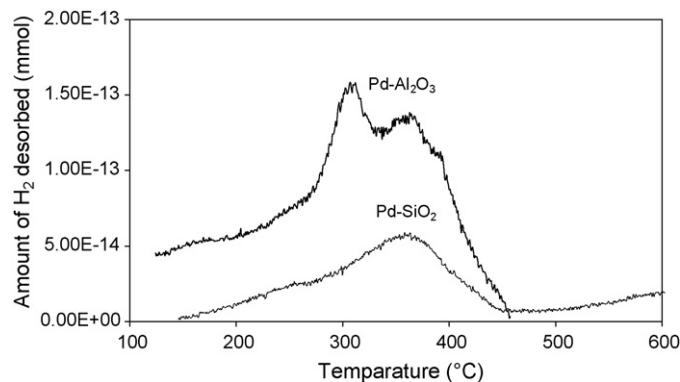The TPD was 25 °C – 10 °C/min – 700 °C (60 min).

Fig. 2. Hydrogen TPD from Pd–SiO$_2$ and Pd-–Al$_2$O$_3$ catalysts.

the nominal metal loading was the same. Furthermore, the Pd crystallites were the largest in Pd–Si–MCM-41 from the three-studied catalyst, while the Pd crystallite size from Pd/SiO$_2$ was not determined, since its activity in the test reaction was low.

The amount of hydrogen desorbed was determined for Pd–SiO$_2$ and for Pd–Al$_2$O$_3$. The latter catalyst exhibited 3.4-fold higher amount of desorbed hydrogen than the former one (Table 2). Furthermore, hydrogen desorption had two maxima in case of Pd–Al$_2$O$_3$, i.e. at 307 °C and at 367 °C indicating that there are two energetically different adsorption sites available on the catalyst surface (Fig. 2), whereas only one temperature maximum for hydrogen desorption was seen for Pd–SiO$_2$.

The acidity of the two supports, Al$_2$O$_3$ and H-MCM-41 was determined with pyridine adsorption (Table 1). The former one exhibited only a small concentration of Brønsted acid sites, whereas their concentration in H–MCM-41 was 12.7-fold that of the former one. In both support materials the concentration of Lewis acid sites was about the same.

3.2. Kinetic results

3.2.1. Catalyst comparison results – definitions

The following definitions were used: initial hydrogenation and acylation rates were defined as the converted amounts (in

mmol) per time unit and catalyst amount, the fractional yield is the ratio between the formed moles of the desired product divided by the initial amount of the reactant, acetophenone; selectivity is a ratio between the moles of the desired product divided by the total molar amount of products. The liquid phase mass balance was calculated by adding the molar amounts of acetophenone, (R,S)-1-phenylethanol, R-1-phenylethyl acetate, ethyl benzene and styrene, water and taking into account stoichiometry in ethanol formation. The mass balance was close to 100%. Only traces of acetic acid were formed.

3.2.1.1. Initial reaction rates and the main reactions.
The total initial reaction rate for acetophenone transformation was determined by calculating the amount of acetophenone converted at the beginning of the experiment per time and per amount of hydrogenation catalyst. During the first 30 min of reaction time the intermediate, (R,S)-1-phenyl ethanol was dehydrated to styrene followed by its fast hydrogenation to ethyl benzene. The initial dehydration rate, i.e. formation rate of styrene and ethyl benzene was additionally calculated. The initial acylation rate was calculated from the amount of the formed R-1-phenyl ethylacetate per time unit and per amount of lipase. The initial rates and acetophenone conversion after 1600 min are given in Table 3.

The total initial transformation rate of acetophenone decreased as follows: Pd–H–MCM-41 > Pd–Al$_2$O$_3$ > Pd–Si–MCM-41 > Pd–SiO$_2$. The Pd particle size of Pd–Al$_2$O$_3$ was 1.8 times larger than in Pd–H–MCM-41 resulting an initial hydrogenation rate being only 34% of the rate obtained with the latter catalyst with smaller Pd particles (Table 3). The third lowest activity was observed for Pd–Si–MCM-41 exhibiting the largest Pd crystallite size of the three studied catalysts in XRD (Table 1). This result indicates that the smaller Pd particles enhanced the hydrogenation of acetophenone. Furthermore, the two most active catalysts possessing Brønsted acidity (Table 1) catalyzed both hydrogenation and dehydration of the formed (R,S)-1-phenylethanol. The initial dehydration rate increased linearly with increasing Brønsted acidity.

The catalyst exhibiting the lowest activity, i.e. Pd–SiO$_2$ was characterized by hydrogen desorption technique and compared with the performance and hydrogen desorption capacity of Pd–Al$_2$O$_3$ (Tables 2 and 3, Fig. 2). The latter catalyst was relatively active in the hydrogenation, while the initial hydrogenation rate over Pd–SiO$_2$ catalyst was 17% of the rate achieved over Pd–Al$_2$O$_3$ catalyst. When correlating this value to the

Table 3
Kinetic results using 125 mg lipase and 125 mg hydrogenation catalyst

Catalyst	Total initial reaction rate (mmol/min/g$_{hydr. cat.}$)	Initial hydrogenation rate (mmol/min/g$_{hydr. cat}$)	Initial dehydration rate (mmol/min/g$_{hydr. cat.}$)	Ratio between the initial dehydration rate to initial hydrogenation rate	Initial acylation rate (mmol/min/g$_{enz.}$)	Conversion after 1600 min (%)
Pd–H–MCM-41	0.44	0.35	0.085	0.24	0.04	92
Pd–Al$_2$O$_3$	0.13	0.12	0.004	0.03	0.002	47
Pd–Si–MCM-41	0.07	0.07	0	0	0.005	15
Pd–SiO$_2$	0.02	0.02	0	0	0.004	7

amounts of hydrogen desorbed, it was clearly visible that the amount of hydrogen desorbed from the former catalyst was only 30% of the value for Pd–Al$_2$O$_3$ indicating that there was a correlation between the initial hydrogenation rate and the amount of hydrogen desorbed form the catalyst. The temperatures at which the maximum amounts of desorbed hydrogen were measured for these two catalysts were about the same thus indicating that only the different amounts of hydrogen available at the catalyst surfaces affected the rates, since the adsorption strengths for hydrogen over the two catalysts should be similar.

The initial dehydration rate was the highest for the most acidic catalyst, i.e. Pd–H–MCM-41 being 21-fold that of the corresponding rate achieved over Pd–Al$_2$O$_3$ (Table 3). The mesoporous support material, H–MCM-41, contained 89 μmol/g Brønsted acid sites (Table 1). Since the concentration of Lewis acid sites in Al$_2$O$_3$ and in H–MCM-41 was about the same, it can be concluded that mainly Brønsted acid sites catalyze dehydration of secondary alcohols. This result deviates from the result of [7], in which gas-phase dehydration of 1-phenylethanol was studied over aluminium oxides. In that work, the main conclusion was that both Brønsted and Lewis acid sites catalyze dehydration of 1-phenylethanol.

The initial acylation rate was the highest over the catalyst exhibiting the highest initial hydrogenation rate, namely Pd–H–MCM-41. This result can be explained by the higher initial concentration of (R,S)-1-phenylethanol obtained over Pd–H–MCM-41 enhancing at the same time the initial acylation rate. When (R,S)-1-phenylethanol was acylated with vinyl acetate over native lipase in *tert*-butyl methyl ether at 30 °C the yield of ester increased by factor 3.2 when increasing the normalized (R,S)-1-phenylethanol concentration from 0.5 to 3.5 [17].

Experimental observations, i.e. formation of styrene, ethyl benzene and acetic acid (see below), allow to present a reaction network for the complex cascade system, containing the supported heterogeneous catalyst and the immobilized enzyme-lipase (Scheme 1).

Hydrogenation of acetophenone over Pd leads to racemic (R,S)-1-phenylethanol and is followed by the consecutive acylation of R-1-phenylethanol to R-1-phenylethyl acetate over lipase. The stoichiometric product of the acylation reaction, ethanol can deactivate enzyme being very hydrophilic [8]. The main side reaction is dehydration of (R,S)-1-phenylethanol to styrene, which occurs on the supports, possessing acidic properties. Due to the availability of hydrogen the subsequent hydrogenation of styrene over Pd catalyst to ethylbenzene is feasible and in fact proceeds very fast, since the amounts of styrene in the reaction mixtures were below 1%.

In order to achieve higher yields of the desired product racemization of S-1-phenylethanol to (R,S)-1-phenylethanol is required. It is known from the literature, that racemization is typically carried out over zeolites [9,10], vanadyl sulfate [11] and Ru-hydroxyapatite [12]. It should be kept in mind, however, that water is formed as a side product in reaction 4 of Scheme 1. Presence of water enhances hydrolysis of R-1-phenyl ethyl acetate over lipase to produce R-1-phenylethanol and acetic acid (step 3 in Scheme 1). This reaction can be also catalyzed by acidic materials [18] indicating that formation of water due to dehydration is not beneficial in the system under investigation, since it facilitates the hydrolysis of the desired product catalyzed either by enzyme or by the acidic catalyst. It means, in essence, that zeolites cannot be used as catalysts for racemization reaction (step 6 in Scheme 1) and some other non-acidic catalysts are needed for the catalytic cascade combining hydrogenation, racemization and acylation reactions avoiding, however, dehydration.

3.2.1.2. Conversions after reaction times. The conversions over four different catalysts after prolonged reaction times decreased as follows: Pd–H–MCM-41 > Pd–Al$_2$O$_3$ > Pd–Si–MCM-41 > Pd–SiO$_2$ (Table 3, Fig. 3).
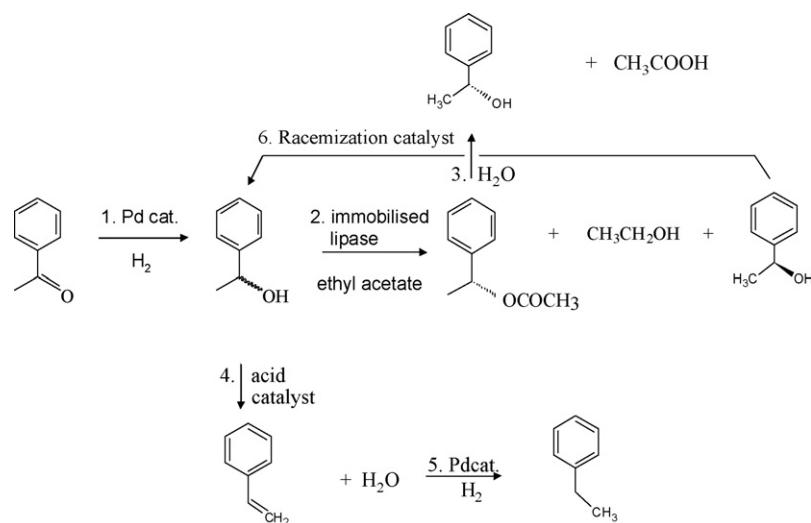
Scheme 1. Reaction scheme for cascade one-pot synthesis of R-1-phenylethyl acetate starting from acetophenone hydrogenation. Reaction steps: (1) hydrogenation of acetophenone to (R,S)-1-phenylethanol; (2) acylation of R-1-phenylethanol to R-1-phenylethyl acetate over immobilized lipase and formation of ethanol; (3) deacylation of R-1-phenylethyl acetate in the presence of water and formation of acetic acid; (4) dehydration of (R,S)-1-phenylethanol in the presence of an acidic catalyst; (5) hydrogenation of styrene to phenylethanol; (6) racemization of S-1-phenylethanol over a racemization catalyst.
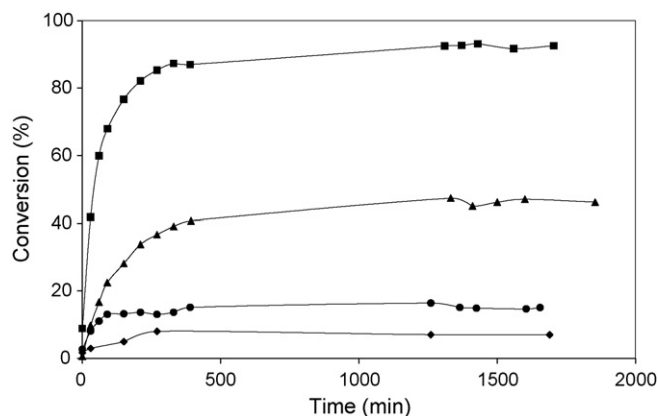
Fig. 3. Conversion of acetophenone as a function of time in one-pot synthesis of *R*-1-phenyl ethylacetate using lipase with (▲) Pd–Al$_2$O$_3$; (♦) Pd–SiO$_2$; (■) Pd–H–MCM-41; and (●) Pd–Si–MCM-41. Conditions: 1 bar hydrogen at 70 °C.

The deactivation of Pd catalysts was clearly visible after prolonged reaction times. There might be several possible reasons for Pd catalysts deactivation, like formation of ethanol as a stoichiometric product in the acylation step, formation of acetic acid in the hydrolysis of the desired product, *R*-1-phenyl ethylacetate (see below), effect of lipase or sintering and/or leaching of Pd. The effect of ethanol was studied by carrying out the hydrogenation of acetophenone over Pd–Al$_2$O$_3$ catalyst without lipase in ethanol. The reaction rate was high and the final conversion was 92% after 1660 min indicating that ethanol is not the reason for deactivation of Pd–Al$_2$O$_3$. Analogous results have been obtained in acetophenone hydrogenation over Pd–Al$_2$O$_3$ in ethanol at 130 °C under 60 bar hydrogen [19]. Additionally, when acetophenone was hydrogenated under the same reaction conditions using 62.5 mg Pd–Al$_2$O$_3$ catalyst without lipase in ethyl acetate the hydrogenation activity was close to zero after 1200 min reaction time corresponding to conversion of 13%. If both Pd–Al$_2$O$_3$ and lipase were used an analogous deactivation of the hydrogenation catalyst occurred. These results indicated that deactivation of the hydrogenation catalyst occurred also in the absence of lipase, therefore leaching of enzyme, which was not studied in the current work, was not the main reason for catalyst deactivation. When comparing, however, the hydrogenation rates in the presence and in the absence of lipase it could be observed that slightly lower rates were achieved in the presence of lipase giving the conversion of 10% after 1200 min. In other words, it can be concluded that the hydrogenation catalyst and the enzyme interfered with each other. Acetic acid is most probably the reason for deactivation of Pd catalyst, although Pd sintering could not be excluded, since in both Pd–SiO$_2$ and Pd–MCM-41 catalysts sintering of Pd was observed [20], when the catalysts were used in liquid phase hydrogenation of 1-hexene in ethanol at 25 °C at 1 bar. In this work [20], Pd nitrate was used as the metal precursor and incipient wetness impregnation was used for introducing Pd. Thereafter, the catalysts were dried and calcined in air at 500 °C for 2 h. In the current work, the catalysts were prepared from palladium nitrate by using vacuum evaporation method, followed by drying and calcination at 400 °C.
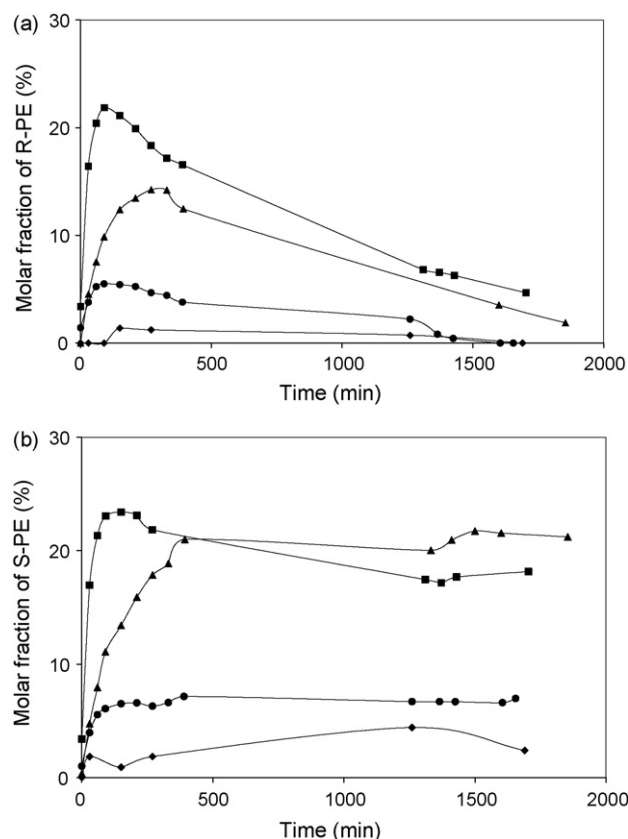

Fig. 4. (a) Fractional yield of *R*-1-phenyl ethanol; (b) *S*-1-phenylethanol using lipase with (▲) Pd–Al$_2$O$_3$; (♦) Pd–SiO$_2$; (■) Pd–H–MCM-41; and (●) Pd–Si–MCM-41. Conditions: 1 bar hydrogen at 70 °C.

3.2.1.3. Product distribution and selectivity. The primary product in acetophenone hydrogenation was (*R,S*)-1-phenylethanol and its formation rate decreased as follows: Pd–H–MCM-41 > Pd–Al$_2$O$_3$ > Pd–Si–MCM-41 > Pd–SiO$_2$ (Fig. 4a and b). The hydrogenation of acetophenone was racemic, since the formation rates for *R*- and *S*-1-phenylethanol were initially the same, as expected. The corresponding maximum fractional yields of *R*-1-phenylethanol were 22%, 14%, 6% and 1% thereafter this enantiomer reacted further either to *R*-1-phenylethyl acetate or via dehydration over acidic sites first to styrene and furthermore via very fast hydrogenation to ethylbenzene, as only traces of styrene could be observed in the reaction mixture. The *S*-enantiomer reacted further only to styrene and to ethylbenzene, since the enantiomeric excess of *R*-1-phenyl ethylacetate was close to 100%. Over Pd catalysts supported on non-acidic SiO$_2$ and Si–MCM-41 as well as over Al$_2$O$_3$ the fractional yields of ethyl benzene was below 1% (Table 4), whereas over Pd–H–MCM-41 the fractional yields of ethylbenzene was 46% after 1600 min (Table 4). The fractional yields of *S*-1-phenylethanol remained constant after reaching its maximum with exception of Pd–H–MCM-41, over which the dehydration took place. Since the amount of *S*-1-phenylethanol remained constant over non-acidic Pd supported catalysts, it can be concluded that Pd did not catalyze racemization.

The acylation of *R*-1-phenylethanol was initially the fastest over Pd–H–MCM-41 most probably due to concentration effect.

Table 4
Selectivity to the desired product and the fractional yield of the side product, ethyl benzene using 125 mg lipase and 125 mg hydrogenation catalyst

Catalyst	Selectivity to R-1-PEAC (%)	Fractional yield of ethyl benzene after 1600 min (%)
Pd–H–MCM-41	7[a], 20 (93)[b]	46
Pd–Al$_2$O$_3$	16[a], 47 (46)[b]	<1
Pd–Si–MCM-41	0[a], 49[c]	<1
Pd–SiO$_2$	47[d]	<1

[a] 40% conversion.
[b] Selectivity after 1700 min, conversion in parenthesis in %.
[c] 15% conversion.
[d] 7% conversion.

The acylation rate over this catalyst, however, decreased to the level of 18% from the initial one after 30 min of reaction time (Fig. 5a), while the rate for styrene formation and its hydrogenation to ethylbenzene was very high and remained constant up to 91 min. On the other hand, the acylation rate over mildly acidic Pd–Al$_2$O$_3$ remained constant until 393 min, declining thereafter. Thus, the highest fractional yields of the desired product, R-1-phenylethyl acetate were achieved over this catalyst, being 22% after 1850 min. The third best catalyst for acylation of R-1-phenylethanol was Pd–Si–MCM-41 yielding to 8% fractional yield of the desired product. The selectivities to R-1-phenylethyl acetate were close to 50%, i.e. to a maximum value, since
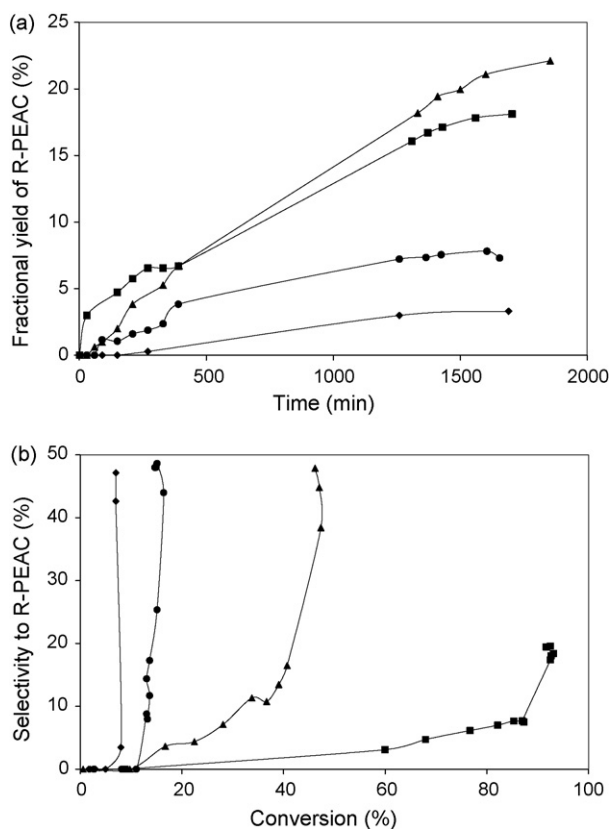

Fig. 5. (a) Fractional yield of R-1-phenylethyl acetate; (b) selectivity of R-1-phenylethyl acetate as a function of acetophenone conversion using lipase with (▲) Pd–Al$_2$O$_3$; (♦) Pd–SiO$_2$; (■) Pd–H–MCM-41; and (●) Pd–Si–MCM-41. Conditions: 1 bar hydrogen at 70 °C.

S-1-phenylethanol was not acylated (Table 4). When plotting selectivity of the desired product as a function of acetophenone conversion, the consecutive reaction pathway is clearly visible for R-1-phenylethyl acetate (Fig. 5b).

The dehydration of (R,S)-1-phenylethanol occurs on the acidic sites of the catalysts. Thus, nearly no dehydration was observed over Pd–SiO$_2$ and over Pd–Si–MCM-41 (Table 3). The dehydration rate was constant over Pd–H–MCM-41 up to 91 min, afterwards declining by 44%, which was due to lowered concentration of (R,S)-1-phenylethanol. The fractional yield of ethyl benzene as a function of R-1-phenylethyl acetate showed that lipase was active in combination with heterogeneous catalysts after prolonged reaction times in spite of the large amounts of ethyl benzene present in the reaction mixture, thus indicating that its presence is not inhibiting the acylation reaction. The enzymatic activity was, however, lowered at prolonged reaction times, since ethanol is formed as a stoichiometric product in the acylation leading to deteriorating activity, as it is known that lipases are more active in hydrophobic solvents [21]. Another reason for the decline of the acylation rate is the formation of water in dehydration of (R,S)-1-phenylethanol. As an example when using 125 mg of Pd–H–MCM-41 the water content of the reaction mixture was 0.4 wt.%, with corresponding fractional yield of ethyl benzene formed after 1700 min being 50%. On the other hand, the presence of trace amounts of water is crucial to guarantee the enzymatic activity, since in hydrophilic solvents the enzyme deactivation occurs due to stripping off the bound water in enzyme. The role of the bound water is thought to preserve the enzyme conformation flexibility [22].

3.3. The effect of hydrogenation catalyst amounts

In the catalyst screening experiments, the same amounts of hydrogenation catalyst and enzyme were used. It turned out that complete conversion of acetophenone was not achieved. The logical idea was to study the influence of the doubled amount of the hydrogenation catalyst in the acylation and dehydration step in order to get a deeper understanding of the reaction mechanism. A non-acidic Pd–SiO$_2$ and slightly acidic Pd–Al$_2$O$_3$ were tested. The initial rates over Pd–SiO$_2$ and Pd–Al$_2$O$_3$ catalysts using 125 mg of lipase and 250 mg of hydrogenation catalyst are given in Table 5. When duplicating the amount of the hydrogenation catalyst the initial hydrogenation rate over Pd–Al$_2$O$_3$ enhanced only by factor 1.3, whereas over Pd–SiO$_2$ the initial rate became slightly more than 2-fold. This result indicates that over the former catalyst there is an interference between the lipase and the hydrogenation catalyst, which is in agreement with experiments showing that faster hydrogenation rates were achieved over Pd–Al$_2$O$_3$ in the absence of lipase compared to the case, when both Pd–Al$_2$O$_3$ and lipase were introduced into the reaction mixture. The interactions between lipase and Pd–SiO$_2$ are probably less strong than between Pd–Al$_2$O$_3$ and lipase. The initial acylation rates were also enhanced when duplicating the amount of hydrogenation catalyst (Tables 4 and 5), but the initial dehydration rate remained unchanged with the double amount of Pd–Al$_2$O$_3$, which was somewhat unexpected. It should, however, be pointed out the dehydration is a consecutive reaction,

Table 5
Kinetic results using 125 mg lipase and 250 mg hydrogenation catalyst

Catalyst	Total initial reaction rate (mmol/ min/$g_{hydr.\ cat.}$)	Initial hydrogenation rate (mmol/ min/$g_{hydr.\ cat}$)	Initial dehydration rate (mmol/ min/$g_{hydr.\ cat.}$)	Ratio between the initial dehydration rate to initial hydrogenation rate	Initial acylation rate (mmol/min/$g_{enz.}$)	Conversion after 1600 min (%)
Pd–Al$_2$O$_3$	0.16	0.156	0.004	0.03	0.004	97
Pd–SiO$_2$	0.05	0.05	0	0	0.03	17

which is clearly visible in the formation of ethyl benzene after prolonged reaction times (see below).

The conversion of acetophenone became 2.1- and 2.4-fold, respectively, when duplicating the amounts of Pd–Al$_2$O$_3$ or Pd–SiO$_2$. The reaction rate over Pd–Al$_2$O$_3$ remained constant up to 90 min of reaction time, declining thereafter. All the hydrogenation catalysts, however, deactivated, since complete conversion of acetophenone was not achieved (Fig. 6). The reason for deactivation of Pd catalysts might be formation of acetic due to lipase catalyzed hydrolysis of *R*-1-phenyl ethyl acetate (see below) [23].

Racemic formation of (*R,S*)-1-phenylethanol was observed as stated above and the fractional yields of *R*- and *S*-1-phenylethanol as a function of reaction time are shown in Fig. 7a and b. The maximum fractional yield of *R*-1-phenylethanol was 38% after 150 min in case of 250 mg of Pd–Al$_2$O$_3$ and 125 mg of lipase (Fig. 7a), whereas with the half amount of the hydrogenation catalyst the corresponding level was 14% after 330 min. This result indicated that it is possible to increase the fractional yield of *R*-1-phenylethanol by increasing the amount of hydrogenation catalyst, i.e. by duplicating the amount of hydrogenation catalyst the fractional yield of *R*-1-phenylethanol increased by factor 2.7. This result would suggest that the acylation reaction should also be enhanced. The results were, however, not as promising, as could be anticipated. Initially the acylation of *R*-1-phenylethanol proceeded at a constant rate up to 400 min of reaction time with 250 mg Pd–Al$_2$O$_3$ and lipase (Fig. 8a) corresponding to the conversion level of 97%. Thereafter, the dehydration of (*R,S*)-1-phenylethanol became the most prominent reaction. The dehydration rate remained constant up to 1650 min, after which

a slight decrease in this rate was observed. The presence of extra water formed in the dehydration of (*R,S*)-1-phenylethanol is not beneficial in the reaction system containing the lipase and an ester, since hydrolysis of ester is catalyzed by lipase forming a carboxylic acid [23]. Formation of propionic acid was confirmed in the acylation of (*R,S*)-1-phenylethanol with vinyl propionate 30 °C with lipase [23]. In the current work, the presence of traces of acetic acid has been verified by GC–MS. Thus, it can be concluded that double amount of Brønsted acid leads to extensive dehydration of (*R,S*)-1-phenylethanol (see below).

The selectivities to *R*-1-phenylethylacetate as a function of conversion using different amounts of Pd–Al$_2$O$_3$ and Pd–SiO$_2$ lipase pairs are shown in Fig. 8b. It can be stated that the acylation of *R*-1-phenylethanol proceeded after prolonged reaction times in all studied systems, with except of the case of 250 mg of Pd–Al$_2$O$_3$ and lipase (Fig. 8b), when the main prod-
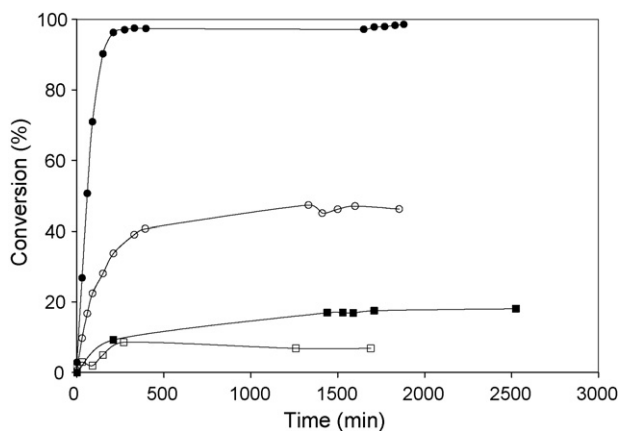

Fig. 6. Conversion of acetophenone using lipase with (●) 250 mg Pd–Al$_2$O$_3$; (○) 125 mg Pd–Al$_2$O$_3$; (■) 250 mg Pd–SiO$_2$; and (□) 125 mg Pd–SiO$_2$. Conditions: 1 bar hydrogen at 70 °C.
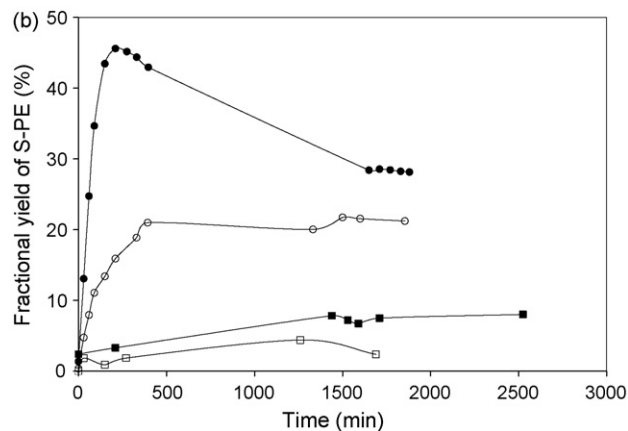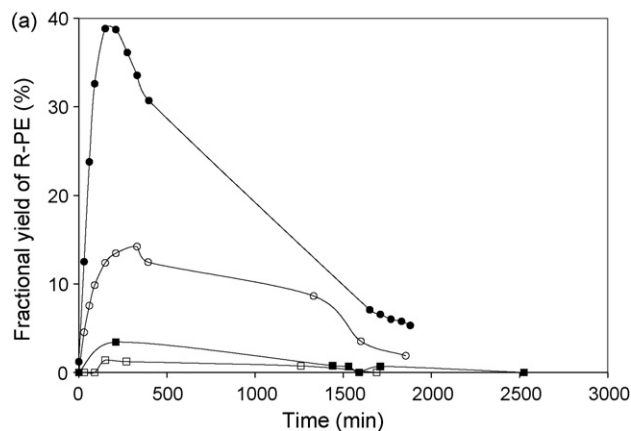

Fig. 7. (a) Fractional yield of *R*-1-phenyl ethanol; (b) *S*-1-phenyl ethanol using lipase with (●) 250 mg Pd–Al$_2$O$_3$; (○) 125 mg Pd–Al$_2$O$_3$; (■) 250 mg Pd–SiO$_2$; and (□) 125 mg Pd–SiO$_2$. Conditions: 1 bar hydrogen at 70 °C.
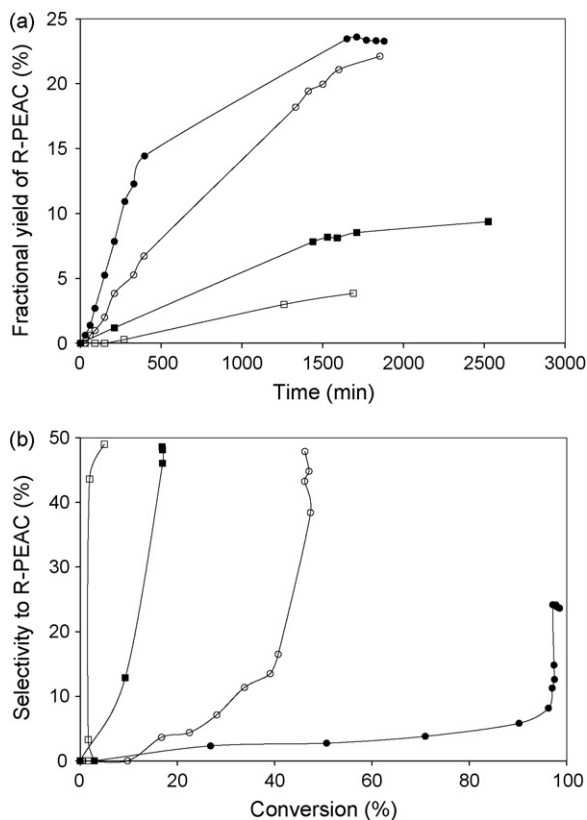
Fig. 8. (a) Fractional yield of *R*-1-phenylethyl acetate as a function of time and (b) selectivity to *R*-1-pehynlethyl acetate as a function of conversion using lipase with (●) 250 mg Pd–Al$_2$O$_3$; (○) 125 mg Pd–Al$_2$O$_3$; (■) 250 mg Pd–SiO$_2$; and (□) 125 mg Pd–SiO$_2$. Conditions: 1 bar hydrogen at 70 °C.

uct was styrene being hydrogenated fast to ethyl benzene with its fractional yield of 38% after 1700 min. When instead using a non-acidic 250 mg Pd–SiO$_2$ and lipase only traces of ethyl benzene were formed. The selectivities to *R*-1-phenyl ethyl acetate after 1700 min were over Pd–Al$_2$O$_3$ and Pd–SiO$_2$ lipase pairs 24% and 49% with conversions of 98% and 18%, respectively. The main conclusion is that the desired 50% fractional yield of *R*-1-phenylethylacetate could not be achieved over the most active catalyst pair, Pd–Al$_2$O$_3$-lipase due to extensive dehydration of (*R,S*)-1-phenylethanol over Brønsted acid sites. The possibility of using larger amount of the hydrogenation catalyst cannot be considered as a viable option since the initial hydrogenation rates were not correlating with the catalyst bulk density, the reason being either mass transfer limitations or detrimental interactions with the enzyme.

4. Conclusions

Four different hydrogenation catalysts together with an immobilized lipase were investigated in one-pot synthesis of *R*-1-phenylethylacetate starting from acetophenone hydrogenation. The experiments were performed in ethyl acetate as an acyl donor using molecular hydrogen at 70 °C. The concentrations of the Brønsted and Lewis acid sites of the supports were determined with pyridine adsorption and sizes of Pd crystallites by XRD. The initial hydrogena-

tion rates decreased with increasing metal particle sizes as follows: Pd–H–MCM-41 > Pd–Al$_2$O$_3$ > Pd–Si–MCM-41. The lowest initial hydrogenation rate was observed over Pd/SiO$_2$. The most promising catalyst pair for the one-pot synthesis of *R*-1-phenylethylacetate was Pd–Al$_2$O$_3$–lipase (Novozym 435) giving under optimal conditions maximally 45% selectivity to *R*-1-phenylethyl acetate at 47% conversion. The acidic catalysts, Pd–H–MCM-41 and Pd–Al$_2$O$_3$ promoted dehydration of the intermediate product (*R,S*)-1-phenylethanol and due to water formation also hydrolysis of *R*-1-phenylethyloacetate, catalyzed either by the lipase or the acidic support.

The observed deactivation of the hydrogenation catalyst could be attributed to the presence of acetic acid being formed in the deacylation step, which in turn was promoted by the presence of water formed in the dehydration of (*R,S*)-1-phenylethanol. Lipase activity decreased after prolonged reaction times due to accumulation of the stoichiometric product ethanol in the reaction mixture. A reaction network was proposed based on the catalytic data.

One of the future directions in developing this type of cascade reaction is to apply non-acidic hydrogenation catalysts in order to avoid water formation and at the same time deacylation. Additionally, application of bases to neutralize acetic acid might increase the catalyst stability. Furthermore, a promising, albeit challenging, option is to combine hydrogenation–acylation and racemization through utilization of non-acidic racemization catalysts.

References

[1] A. Bruggink, R. Schoevaart, T. Kieboom, Org. Proc. Res. Dev. 7 (2003) 622–640.
[2] H.M. Jung, J.H. Koh, M.-J. Kim, J. Park, Org. Lett. 2 (2000) 2487–2490.
[3] U. Hanefeld, Org. Biomol. Chem. 1 (2003) 2405–2415.
[4] H.R. Hobbs, B. Kondor, P. Stephenson, R.A. Sheldon, N.R. Thomas, M. Poliakoff, Green Chem. 8 (2006) 816.
[5] A. Drelinkiewicza, A. Waksmundzka, W. Makoski, J.W. Sobczak, A. Król, A. Zięba, Catal. Lett. 94 (2004) 143–156.
[6] F. Gao, A.D. Allian, H. Zhang, S. Cheng, M. Garland, J. Catal. 241 (2006) 189–199.
[7] R.G. Romanova, A.A. Lamberov, I.G. Shmelev, Kin. Catal. 45 (3) (2004) 422–428.
[8] K. Faber, Biotransformations in Organic Chemistry, Springer, Berlin, 1992, IX, 319.
[9] S. Wuyts, K. De Temmerman, D.E. De Vos, P.A. Jacobs, Chem. Comm. (2003) 1928–1929.
[10] S. Wuyts, K. De Temmerman, D.E. De Vos, P.A. Jacobs, Chem. Eur. J. 11 (2005) 386–397.
[11] S. Wuyts, J. Wahlen, P.A. Jacobs, D.E. De Vos, Green Chem. 9 (2007) 1104–1108.
[12] S. Wuyts, D.E. De Vos, F. Verpoort, D. Depla, R. De Gryse, P.A. Jacobs, J. Catal. 219 (2003) 417–424.
[13] J. S. Beck, US Patent 5057296 (1991).

[14] C. T. Kresge, M.E. Leonowicz, W.J. Roth, J.C. Vartuli, US Patent 5098 684 (1992).

[15] A. Bernas, N. Kumar, P. Mäki-Arvela, N.V. Kulkova, B. Holmbom, T. Salmi, D.Yu. Murzin, Appl. Catal. A: Gen. 245 (2003) 257–275.

[16] C.A. Emeis, J. Catal. 141 (1993) 347–354.

[17] Y. Ikeda, R. Nozaki, Y. Kurokawa, J. Chem. Technol. Biotechnol. 77 (2001) 86–91.

[18] A. Hilton, R.R. Myers, J. Am. Chem. Soc. 64 (1942) 2362–2365.

[19] M. Bejblová, P. Zámostný, L. Červený, J. Čejka, Collect. Czech. Chem. Commun. 68 (2003) 1969–1984.

[20] J. Panpranot, K. Pattamakomsan, P. Praserthdam, React. Kinet. Catal. Lett. 86 (1) (2005) 141–147.

[21] E. Cernia, C. Palocci, S. Soro, Chem. Phys. Lipids 93 (1998) 157–168.

[22] L.S. Chua, M.R. Sarmidi, J. Mol. Catal. B: Enzym. 38 (2006) 551–556.

[23] F.J. Hernández-Fernández, A.P. de los Ríos, F. Tomás-Alonso, D. Gómez, M. Rubio, G. Víllora, Chem. Eng. Proc. 46 (2007) 818–824.