Res Chem Intermed (2010) 36:193–210
DOI 10.1007/s11164-010-0129-2

Mechanism of the chemo–bio catalyzed cascade synthesis of *R*-1-phenylethyl acetate over Pd/Al_2O_3, lipase, and Ru-catalysts

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Received: 22 May 2009 / Accepted: 19 November 2009 / Published online: 19 March 2010

Abstract One-pot synthesis of *R*-1-phenylethyl acetate was investigated starting from acetophenone hydrogenation performed over Pd/Al_2O_3 and $PdZn/Al_2O_3$ catalysts followed by acylation of the intermediate secondary alcohol, *R*-1-phenylethanol, over an immobilized lipase. Furthermore, the performance of a third type of catalyst, Ru supported on hydroxyapatite (HAP) was evaluated for racemization of *S*-1-phenylethanol in one pot together with the two other catalysts. The main objectives of this work were to separate the effects of different catalysts and to reveal the reaction mechanism. For this purpose not only acetophenone, but also (*R,S*)-1-phenylethanol, *S*-1-phenylethanol, *R*-1-phenylethyl acetate, and styrene were used as reactants in combination with Pd/Al_2O_3, lipase and Ru/HAP as catalysts. The results revealed that the main side product, ethylbenzene, was formed in two different ways, via dehydration of (*R,S*)-1-phenylethanol to styrene, followed by its rapid hydrogenation to ethylbenzene, and via debenzylation of the desired product, *R*-1-phenylethyl acetate to ethylbenzene. The true one-pot synthesis, however, was demonstrated over Shvo's catalyst, but Ru/HAP was not sufficiently active in the racemization step. Ru/Al_2O_3 was a promising catalyst for racemization of *S*-1-phenylethanol and for dynamic kinetic resolution of (*R,S*)-1-phenylethanol, when using only small amounts of the acyl donor ethyl acetate. The challenge in

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racemization is that the activity of heterogeneous Ru catalysts was inhibited by esters.

Keywords Chemo–bio cascade · Acetophenone hydrogenation · Acylation · Pd · Ru · Lipase

Introduction

Cascade catalysis is of high interest in synthesizing organic molecules, because it has several benefits compared with traditional multi-step synthesis [1]. In cascade reactions the basic idea is to perform several reaction steps in one pot. This approach is, however, demanding if the catalysts are of different nature, being chemical and enzymatic. The optimum reaction conditions can be very different for different catalysts and furthermore, they can interrelate indicating that some undesirable side reactions can occur.

One very demanding reaction is the combination of three different catalysts in one-pot, which is the case in the synthesis of *R*-1-phenylethyl acetate starting from hydrogenation of acetophenone over a heterogeneous supported metal catalyst, kinetic resolution of the intermediate secondary alcohol, *R*-1-phenylethanol, over an enzyme, and racemization of *S*-1-phenylethanol over another heterogeneous catalyst. This reaction has been successfully demonstrated using a homogeneous Ru complex as a hydrogenation and racemization catalyst and with lipase used for kinetic resolution [2], and confirmed in this work also. As far as we are aware there are no reports in which all three reactions have been successfully performed over heterogeneous catalysts, which is industrially more attractive than use of the homogeneous counterparts.

Hydrogenation and kinetic resolution in one-pot can be achieved by use of a low acidity Pd/Al_2O_3 catalyst for hydrogenation and an immobilized lipase for resolution [3–6]. The drawback in this approach was, however, the lack of racemization step, which limiting the yield of the desired product to 50%. It would thus be desirable to develop an active racemization catalyst for *S*-1-phenylethanol for the one-pot synthesis of *R*-1-phenylethyl acetate starting from acetophenone hydrogenation (Fig. 1).

Racemization of secondary alcohols has been demonstrated over homogeneous Ru-complex catalysts [7]. The following reaction mechanism has been proposed for this reaction [8]. In the first step an Ru–alcoholate species is formed, and in the next step β-hydride elimination results in the formation of the corresponding ketone, in this case acetophenone. This step, in which deprotonation of the alcohol occurs, is promoted under alkaline conditions. In the third step the ketone is reduced to an enantiomeric alcohol with the aid of Ru–hydride species. There are, however, other reaction mechanisms also, e.g. the one in which racemization occurs via isomerization, with Ru–alcoholate as an intermediate and the ketone is produced via complete of an alcohol. This was proposed as the operative mechanism because in the β-hydride elimination mechanism addition of acetophenone did not suppress formation of the ketone [9].

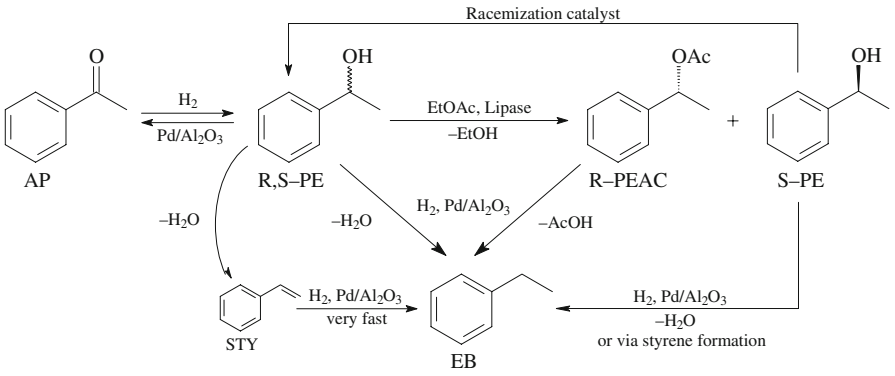

Fig. 1 Reaction scheme for one-pot synthesis of *R*-1-phenylethyl acetate starting from acetophenone hydrogenation. Notation: *AP* acetophenone, *R,S-PE* (*R,S*)-1-phenylethanol, *R-PEAC* *R*-1-phenylethyl acetate, *S-PE* *S*-1-phenylethanol, *STY* styrene, *EB* ethylbenzene

Racemization of secondary alcohols has been demonstrated over several types of heterogeneous catalysts, for example zeolites [10] and supported Ru catalysts [8, 9]. Zeolites are too acidic to be used as catalysts in one-pot synthesis of *R*-1-phenylethyl acetate, in which dehydration of (*R,S*)-1-phenylethanol is catalyzed by strongly acidic catalysts. Two different types of Ru catalysts have been reported to be active in racemization of *S*-1-phenylethanol, i.e. Ru supported on hydroxyapatite (HAP) [8] and on Al_2O_3 [11]. The alkaline hydroxyapatite has been reported to promote deprotonation of *S*-1-phenylethanol during racemization. The active species in racemization was proposed to be Ru^{3+} [8].

One objective of this work was to separate the effects of different catalysts in one-pot synthesis of *R*-1-phenylethyl acetate from acetophenone hydrogenation. One undesired reaction is formation of ethylbenzene and the question which should be answered is whether ethylbenzene is formed via dehydration of (*R,S*)-1-phenylethanol, followed by its rapid hydrogenation to ethylbenzene, or by debenzylation of *R*-1-phenylethyl acetate over Pd species. The following experiments were performed:

(1) hydrogenation of acetophenone over Pd/Al_2O_3 and over Ru/HAP;
(2) hydrogenation and kinetic resolution over Pd/Al_2O_3 and lipase; and
(3) hydrogenation and dynamic kinetic resolution using Pd/Al_2O_3, lipase, and Ru/HAP.

Furthermore, the different catalysts can affect the reaction intermediates in an unexpected way and thus their effects were studied in transformations of (*R,S*)-1-phenylethanol over Pd/Al_2O_3 and Al_2O_3, styrene hydrogenation over Pd/Al_2O_3, and reactions of *R*-1-phenylethyl acetate over Al_2O_3 and lipase. Apart from these experiments, racemization of *S*-1-phenylethanol was also investigated over three different types of supported Ru catalysts:

(1) Ru/HAP calcined and prereduced;
(2) Ru/HAP only calcined; and
(3) Ru/Al_2O_3 prepared by the method reported elsewhere [12, 13].

For comparison with Pd/Al_2O_3 as catalyst few experiments were also performed with $Pd–Zn/Al_2O_3$ catalyst together with lipase.

Experimental

Kinetic experiments

Three different types of catalysts were tested in acetophenone hydrogenation and its (dynamic) kinetic resolution. Pd/Al_2O_3 was used as a hydrogenation catalyst. It was prepared by vacuum evaporation impregnation techniques described elsewhere [4] using palladium nitrate as a Pd source. A commercial immobilized lipase, Novozym 435 was used for kinetic resolution of *R*-1-phenylethanol. Two different supported Ru catalysts were investigated as racemization catalysts, namely Ru supported on hydroxyapatite and Ru prepared by an ion-exchange method.

Hydroxyapatite was prepared by the method used in Ref. [14]. Shvo's catalyst (Sigma) (1-hydroxytetraphenylcyclopentadienyl(tetraphenyl-2,4-cyclopentadien-1-one)-μ-hydrotetracarbonyldiruthenium(II)) was also applied in one-pot synthesis of *R*-1-phenylethyl acetate at 70 °C in ethyl acetate in flowing hydrogen, using an initial acetophenone concentration of 0.02 mol/L.

Hydrogenation of acetophenone (Fluka) was performed in a glass reactor with the liquid phase volume of 250 mL using ethyl acetate as solvent and as an acetyl group donor. Before the reaction the catalyst was reduced at either 100 or 200 °C. Thereafter the reaction was started by injecting the solvent containing the acetophenone, at the initial concentration of 0.02 M, together with lipase (Novozym 435) into the reactor. Typically, 250 mg Pd/Al_2O_3 in the presence or absence of racemization catalyst, Ru/HAP (125 mg) and lipase (125 mg) were used. Furthermore, catalytic transformations of *S*-1-phenylethanol (Aldrich, 97%) and (*R,S*)-phenylethyl acetate (Acros Organics, >98%) were investigated.

The reaction mixture was analyzed by gas chromatography with a chiral column (Supelco Beta-Dex 225 (30 m × 250 μm × 0.25 μm)) using a flame ionization detector. The temperature program was: 66 °C (5 min) – 20 °C/min – 111 °C (10 min) – 20 °C/min – 190 °C. The products were identified by GC–MS (GC: 6890N Network GC Systems, Agilent technologies; column: Agilent DB-Petro (50 m × 200 μm × 0.5 μm); mass spectrometer: Agilent 5973 Network).

Catalyst preparation and characterization

Pd/Al_2O_3 (5 wt%) was prepared by impregnation of alumina with an aqueous solution of palladium nitrate (Degussa) as palladium source. Thereafter, it was dried at 110 °C and calcined in a muffle oven.

Complex $PdZn(OAc)_4.H_2O$ for $Pd–Zn/Al_2O_3$ (2 wt% Pd, 0.63 wt% Zn) catalyst was prepared as follows [15]. Palladium acetate (Sigma–Aldrich, 99.9+ % metal basis) and zinc acetate (Fluka, >99.5% (KT)) were used without further purification. Glacial acetic acid was purchased from Merck (100%, GR for analysis). To a 25-mL round-bottomed flask equipped with a magnetic stirrer and reflux condenser, flushed with Ar

for 10 min before use, $Zn(OAc)_2.2H_2O$ (220 mg, 1 mmol) and $Pd(OAc)_2.2H_2O$ (224 mg, 1 mmol) were loaded followed by addition of glacial acetic acid (10 mL). The mixture was stirred under gentle reflux until complete dissolution of the salts and then for 40 min longer. The resulting solution was filtered through a Schott filter (#3) and evaporated on a rotary evaporator (8 mbar, 30 °C). The remaining acetic acid was removed by evaporation of the resulting mixture with benzene (5 times × 15 mL, 30 mbar, 30 °C) affording a sand-colored crystalline powder. The presence of the complex was confirmed by ^{1}H NMR (600.13 MHz, $CDCl_3$): 2.02 (s, 4OAc).

The Pd–Zn/Al_2O_3 catalyst was prepared using the wetness-incipient technique [16]. The above mentioned complex $PdZn(OAc)_4.H_2O$ (82.6 mg) was dissolved in absolute methanol (3 mL) at room temperature. The resulting solution was added dropwise to alumina (UOP) (1 g) and the resulting mixture was thoroughly stirred to a homogeneous paste and left overnight at room temperature. The catalyst prepared in this way was pretreated before the reaction by use of the following temperature procedure: Ar flow, 5 °C/min to 80 °C and kept for 2 h, switched to H_2, 5 °C/min to 250 °C and kept for 1 h, switched to Ar and kept for 20 min at 250 °C, cooling to room temperature in Ar flow.

Ru on HAP (1.75 wt% Ru) was prepared by the vacuum-impregnation method from hydroxyapatite and a solution of $Ru(acac)_3$ in toluene. Hydroxyapatite (HAP) was synthesized by a method described elsewhere [14]. HAP (2 g) was added to a solution of ruthenium acetylacetonate (140 mg, Aldrich, 97%) in toluene (60 mL, J.T. Baker) and the reddish slurry was vigorously stirred for 4 h at ambient temperature. The solvent was removed at reduced pressure and the solid material obtained was dried under vacuum followed by calcination in a muffle oven (320 °C, 12 h, heating rate 5 °C/min, and normal atmosphere) resulting in a beige powder (1.8 g). The ion-exchanged Ru/HAP was prepared using $RuCl_3{\cdot}xH_2O$ as an Ru source, using a method described elsewhere [8]. Ru/Al_2O_3 (4 wt%) catalyst was prepared by a method described elsewhere [12, 13].

Catalysts were characterized by nitrogen adsorption to determine the specific surface area, temperature programmed reduction, and CO chemisorption and TEM to elucidate the metal particle size and metal dispersion. Nitrogen adsorption was measured by use of Carlo Erba equipment; the BET equation was used for determination of the specific surface area and the DH method for determination of pore-size distribution. Temperature-programmed reduction of the catalyst was performed with AutoChem Micromeritics using the programs: 10 °C/min − 400 °C for Ru/HAP and Ru/Al_2O_3 and 5 °C/min − 400 °C for Pd/Al_2O_3. Metal particle size was investigated by TEM and by CO-chemisorption, using EFTEM: LEO 912 Omega and AutoChem 2900 (Micromeritics) equipment, respectively.

Results and discussion

Catalyst characterization results

Metal dispersion and average metal particle sizes were measured by TEM, by CO chemisorption, and by XRD techniques. The mean Pd particle sizes of Pd/Al_2O_3

catalyst reduced either at 100 °C or at 200 °C, determined by XRD, were 7.1 nm [6] and 8.6 nm, respectively, indicating that slight sintering of Pd particles occurred after reduction at 200 °C. The corresponding average Pd particle size after reducing the catalyst at 200 °C was determined by TEM (Fig. 2), and was 4.2 nm. The Ru/HAP had 4 nm average Ru particle size after reduction at 200 °C for 30 min, corresponding to metal dispersion of 32%. It should, however, be pointed out that at this temperature Ru is not completely reduced, which was confirmed by temperature-programmed reduction (see below). CO is thus adsorbed by Ru^{3+} species forming surface carbonyl species. For Ru/Al_2O_3 catalyst the average metal particle size was determined from a TEM image to be 1.3 nm (picture not shown here).

The BET specific surface area of Pd/Al_2O_3, measured by nitrogen adsorption, was 306 m^2/g. The alumina support used in Pd/Al_2O_3 contained low concentrations of Bronsted and Lewis acid sites—7 and 156 $\mu mol/g_{cat.}$, respectively [17].

Temperature programmed reduction was used to determine the temperature at which the metal was reduced (Fig. 3). The reduction of palladium on alumina occurred close to 71 °C, whereas Ru/HAP was reduced at 174 °C. It should, however, be pointed out here that there was a second hydrogen-consuming peak occurring at 268 °C indicating that Ru was not totally in the metallic state below 200 °C. The ion-exchange Ru species supported on hydroxyapatite needed slightly higher reduction temperatures than the Ru/HAP catalyst prepared by the impregnation method. The reduction temperature for Ru in 4 wt% Ru/Al_2O_3 was shown to be 137 °C according to TPR, indicating, analogously to Ref. [18], that it remained as Ru^{n+} during the hydrogenation of acetophenone at 70 °C. Furthermore, the reduction of Pd in $Pd–Zn/Al_2O_3$ catalyst occurred at 115 °C, whereas a high-temperature peak was obtained at 351 °C; this most probably indicates reduction of Zn species. It was, however, confirmed by XAFS that alloy formation had already occurred at 250 °C [16].

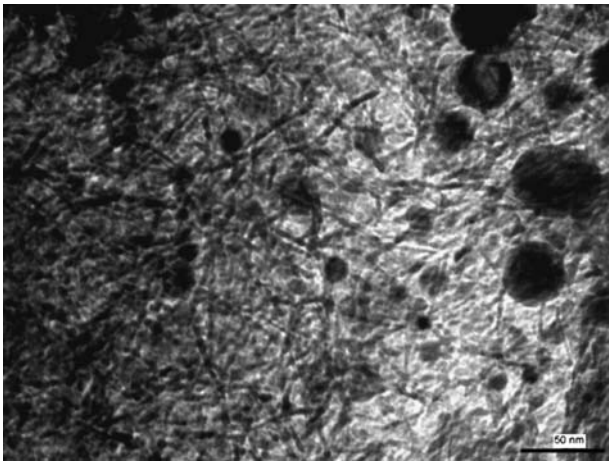

Fig. 2 TEM picture of Pd/Al_2O_3 catalyst reduced at 200 °C

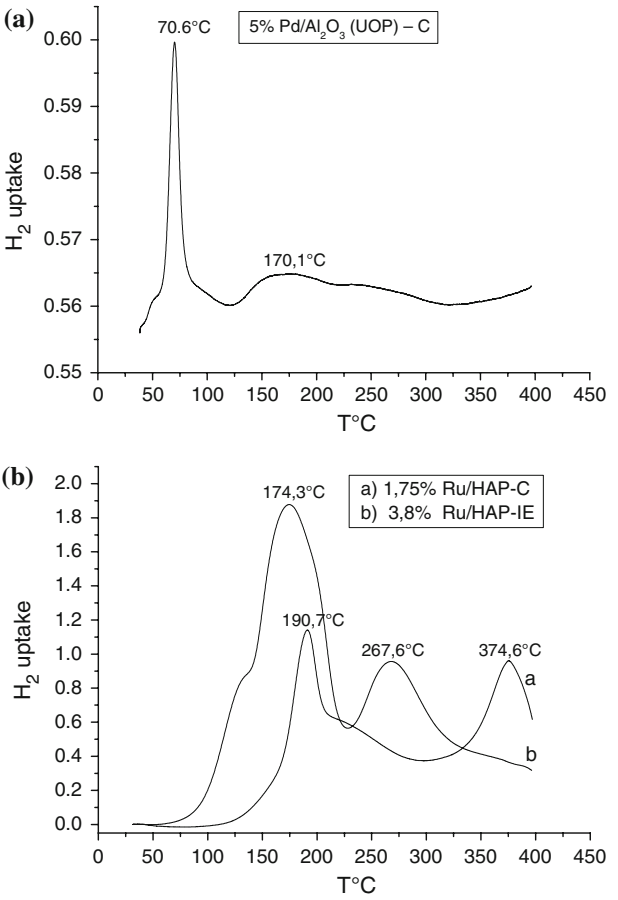

Fig. 3 Temperature programmed reduction from **a** Pd/Al_2O_3 and **b** Ru/HAP

Results from the kinetic studies

The mechanism in one-pot synthesis of *R*-1-phenylethyl acetate starting from acetophenone hydrogenation was of interest in this work. To reveal the reaction mechanism, the following types of kinetic studies were performed: acetophenone hydrogenation, acetophenone hydrogenation combined with kinetic resolution, one-pot synthesis of *R*-1-phenylethyl acetate, and some transformations of reaction intermediates and products over different catalysts. The catalysts investigated were: Pd-100 and Pd-200, which are Pd/Al_2O_3 catalysts reduced at 100 °C and 200 °C, respectively, for 30 min, and Pd-100–Ru and Pd-200–Ru, which are a mixture of Pd/Al_2O_3 and Ru/HAP reduced at either 100 °C or 200 °C, respectively. The notation Lip stands for lipase in, e.g., Pd-100–Lip. Furthermore, a catalytic system containing three catalysts, i.e. Pd-200–Ru–Lip indicating Pd/Al_2O_3, Ru/HAP reduced at 200 °C for 30 min, and lipase was applied. Results from the different reaction types are presented below.

Hydrogenation of acetophenone

The kinetics of hydrogenation of acetophenone were investigated using Pd/Al_2O_3 catalysts reduced at either 100 °C or 200 °C for 30 min and also using Pd-100–Ru and Pd-200–Ru. The lowest initial hydrogenation rate was observed for Pd-100, despite the fact the Pd was reduced at 71 °C according to TPR (see above). The hydrogenation, however, proceeded faster after about 90 min. This result indicated that part of Pd was being reduced during the initial induction time and that 30 min reduction time at 100 °C was not enough to reduce Pd completely. The initial rates decreased with the three more active catalysts in the order: Pd-100–Ru > Pd-200 > Pd-200–Ru. Furthermore, when conversion levels after 200 min (Table 1; Fig. 4a) over different catalysts are compared it can be observed that the most active system catalyst was Pd-100–Ru. This result can be explained by the fact that Pd was slightly sintered according to XRD results, after its reduction at 200 °C. The question why Pd-100–Ru was the most active catalyst combination is not trivial to answer, because Ru/HAP catalyst was inactive in the hydrogenation of acetophenone in ethyl acetate as solvent (Table 1, entry 8). At the moment we consider the higher activity of the Pd-100–Ru system to be explained by lower deactivation of the catalyst mixture compared with Pd-200. Catalyst deactivation occurs because of deacylation of a target phenylethyl acetate molecule and hydrogenolysis of intermediate *R,S*-phenylethanols. Additionally only low hydrogenation activity of Ru/HAP was achieved for acetophenone using toluene as solvent (Table 1, entry 9).

The formation of *R*-1-phenylethanol as a function of temperature, shown in Fig. 4b, follows the same order in the formation rates as obtained for acetophenone

Table 1 Kinetics of acetophenone hydrogenation, kinetic resolution, and dynamic kinetic resolution over Pd/Al_2O_3, Ru/HAP and lipase at 70 °C in ethyl acetate

Entry	Catalyst	Init. rate (mmol/min/g_{Me})	Conversion after 200 min (%)	Selectivity of *R*-PEAC (%) at 70% conversion[c]	Selectivity of ethylbenzene (%) at 70% conversion[d]
1	Pd-100	0.6	55 (98)	0	1 (11)
2	Pd-200	2.4	62 (97)	0	1 (5)
3	Pd-100–Lip	1.1	43 (98)	6 (16)	1 (17)
4	Pd-200–Lip	1.0	23 (78)	23[e]	1 (8)
5	Pd-100–Ru	4.8	95 (98)	0	4 (76)
6	Pd-200–Ru	1.7	64 (98)	0	1 (12)
7	Pd-200–Ru–Lip	0.9	64 (98)	10 (32)	1 (37)
8	Ru/HAP[a]	0	Inactive	0	–
9	Ru/HAP[a, b]	Very low	8	0	0

[a] Catalyst prereduced at 200 °C

[b] Toluene as solvent

[c] After 1200 min in parentheses

[d] At the conversion level of 97% in parentheses

[e] Conversion only 78% after 1200 min

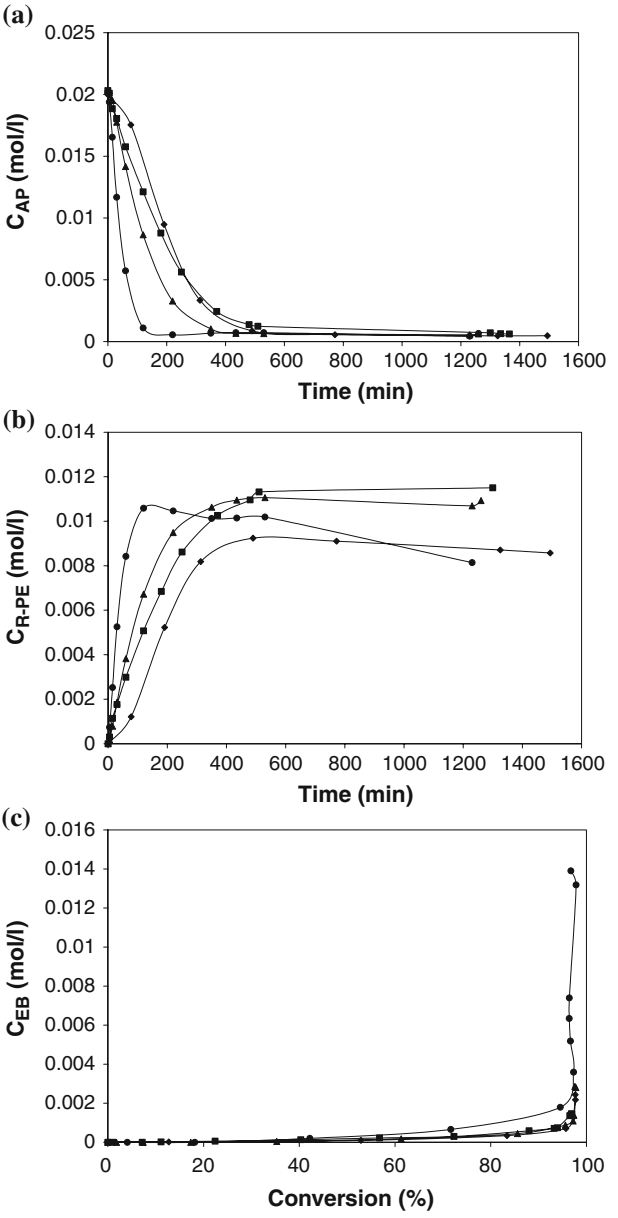

Fig. 4 Kinetics of hydrogenation of acetophenone, **a**, *R*-1-phenylethanol, **b**, and ethylbenzene, **c**, as a function of conversion over Pd/-100 (◆), Pd-200 (■), Pd-100–Ru (●) and Pd-200–Ru (▲)

reaction rates. Analogous curves were achieved for *S*-1-phenylethanol because of racemic hydrogenation and dehydration of the secondary alcohol. In these experiments there was no lipase present and thus the decrease in the concentration of *R*-1-phenylethanol over Pd-100–Ru catalyst was because of dehydration of the

secondary alcohol to styrene followed by its rapid hydrogenation to ethylbenzene. This is also apparent in Fig. 4c, in which the formation of ethylbenzene is presented as a function of acetophenone conversion. The selectivity to ethylbenzene at the 97% conversion level was about 76% (Table 1). It can thus be concluded that the presence of Ru/HAP catalyzed dehydration of (*R,S*)-1-phenylethanol.

When comparing ethylbenzene formation over Pd-100 and Pd-200 catalysts, it was clearly visible that over smaller Pd particles (Pd-100) more ethylbenzene was formed compared with larger Pd particles (Pd-200) (Fig. 4b; Table 1). Analogously in the hydrogenation of acetophenone over Pd/C catalysts in the liquid phase using hexane as a solvent the main product was ethylbenzene when the reaction temperature exceeded 85 °C whereas only 40% ethylbenzene was achieved at 60 °C [19].

The activity of Pd/Al_2O_3 after prolonged reaction times in acetophenone hydrogenation was investigated by adding 2.2 mmol acetophenone three times during the reaction (Fig. 5). This result indicated that the Pd/Al_2O_3 catalyst was active in acetophenone hydrogenation after prolonged reaction times.

Hydrogenation of acetophenone and kinetic resolution of *R*-1-phenylethanol

In acetophenone hydrogenation combined with kinetic resolution two different catalyst systems were compared—Pd-100–Lip and Pd-200–Lip (Table 1, entries 3, 4; Fig. 6). The initial hydrogenation rates for both catalysts were about the same. The reaction proceeded, however, much faster over the former catalyst system than over the latter (Fig. 6a) indicating that catalyst deactivation was more prominent for Pd-200–Lip than for Pd-100–Lip.

The conversion level of Pd-200–Lip was only 78% after 1200 min reaction time, whereas close to 100% conversion was achieved over Pd-100–Lip (Table 1, entries 3, 4). The reason for the more severe deactivation for Pd-200–Lip catalyst compared with Pd-100–Lip is the faster debenzylation of *R*-1-phenylacetate over Pd-200–Lip

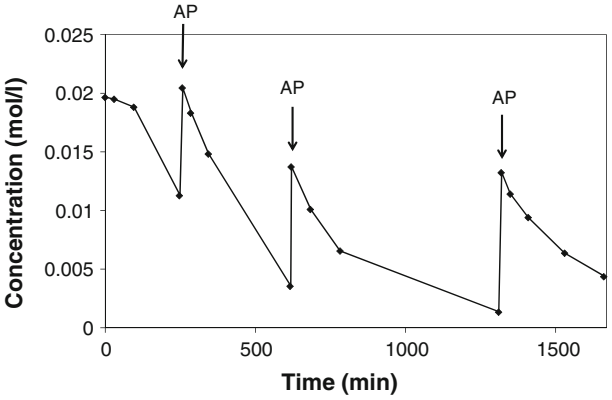

Fig. 5 Hydrogenation of acetophenone (AP) over Pd/Al_2O_3 catalyst in ethyl acetate at 70 °C. The initial concentration of acetophenone was 0.02 mol/L and three batches of acetophenone (2.2 mmol) were added after prolonged reaction times

(Fig. 6d), which enhanced coking of the Pd-200–Lip catalyst. At the same time the rate of acylation was much faster over Pd-200–Lip than over Pd-100–Lip (Fig. 6c).

Mechanistically, it was interesting to observe that ethylbenzene formation was more selective in the presence of lipase than in its absence (Table 1, entry 1, 3). This result indicates that the debenzylation of *R*-1-phenylethyl acetate is faster than the dehydration of the secondary alcohol (*R,S*)-1-phenylethanol to styrene followed by its hydrogenation to ethyl benzene.

Hydrogenation of acetophenone and dynamic kinetic resolution of *R*-1-phenylethanol

One-pot synthesis of *R*-1-phenylethyl acetate from acetophenone was investigated over the Pd-200–Ru–Lip catalyst system (Table 1, entry 7; Fig. 7a). Hydrogenation of acetophenone proceeded with the same rates over Pd-200–Ru and over Pd-200–Ru–Lip, indicating that lipase had no effect on the hydrogenation of acetophenone.

The formation of *R* and *S*-1-phenylethanol proceeded faster over Pd-200–Ru and Pd-200–Ru–Lip than over Pd-200–Lip (Fig. 7a). No racemization, however, occurred over Pd-200–Ru, because the level of *S*-1-phenylethanol remained constant after prolonged reaction times. Separate racemization experiments (see below) confirmed this result. When using the Pd-200–Ru–Lip combination of catalysts, the concentration of *R*-1-phenylethanol was maximum after approximately 310 min, after which it reacted further to both *R*-1-phenylethyl acetate and ethylbenzene

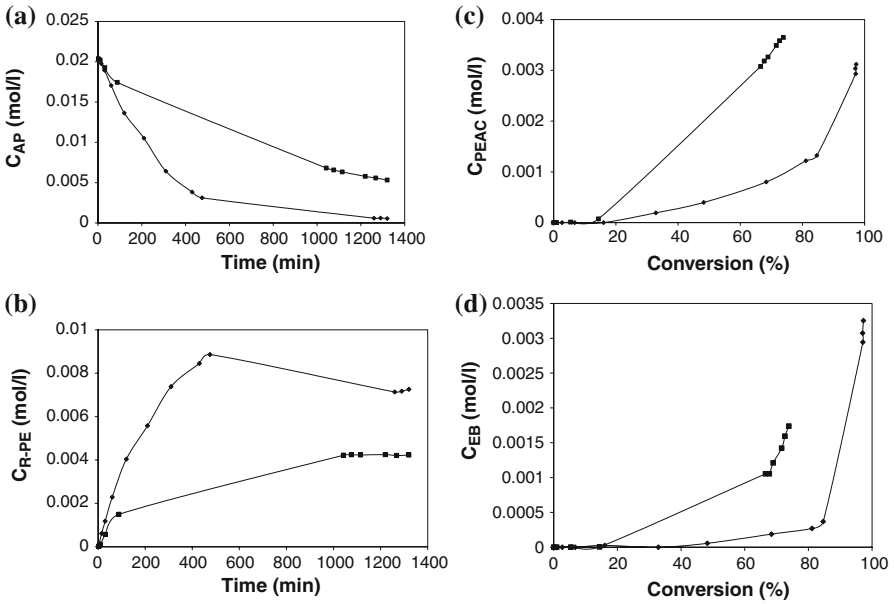

Fig. 6 Kinetics of hydrogenation of acetophenone, **a**, and formation of *R*-1-phenylethanol, **b**, *R*-1-phenylethyl acetate, **c**, and ethylbenzene, **d**, as a function of conversion over Pd/Al_2O_3-100–lipase (◆) and over Pd/Al_2O_3-200–lipase (■)

(Fig. 7c, d). In contrast, the rate of formation of (*R,S*)-1-phenylethanol decreased after 90 min reaction time because of deactivation of the Pd/Al_2O_3 catalyst. The reason for this behavior was coking of the Pd catalyst. The initial hydrogenation activity of Pd-200–Lip was high, but hydrogenation activity decreased relatively rapidly because of debenzylation of *R*-1-phenylethyl acetate. At the same time the rate of formation of ethylbenzene increased, which is clearly visible from the low value (12) of the ratio of the initial rate of formation of (*S,R*)-1-phenylethanol to that of ethylbenzene (Table 2, entry 2). The two other catalyst systems, i.e. Pd-100–Lip and Pd-200–Ru–Lip, exhibited high initial rates of formation of secondary alcohols compared with that of ethylbenzene.

Comparison of the kinetics of formation of *R*-1-phenylethyl acetate and ethylbenzene is of interest for Pd-100–Lip, for Pd-200–Lip, and for Pd-200–Ru–Lip mixtures (Table 2). The ratio of the initial rate of formation of 1-phenylethyl acetate to that of ethylbenzene decreased in the order Pd-200–Ru–Lip > Pd-100–Lip > Pd-200–Lip for the three combinations tested. This result, i.e. that more of the desired product, *R*-1-phenylethyl acetate, was formed over Pd-200–Ru–Lip than over the other catalyst systems, can be explained by the fact that there are more adsorption sites available for reaction intermediates and thus the debenzylation of *R*-1-phenylethyl acetate, which is catalyzed by Pd, is retarded because of the lowered relative concentration of Pd in Pd-200–Ru–Lip compared with the Pd-200–Lip system. Furthermore, Ru/HAP was inactive in transforming *R*-1-phenylethyl acetate (see below).

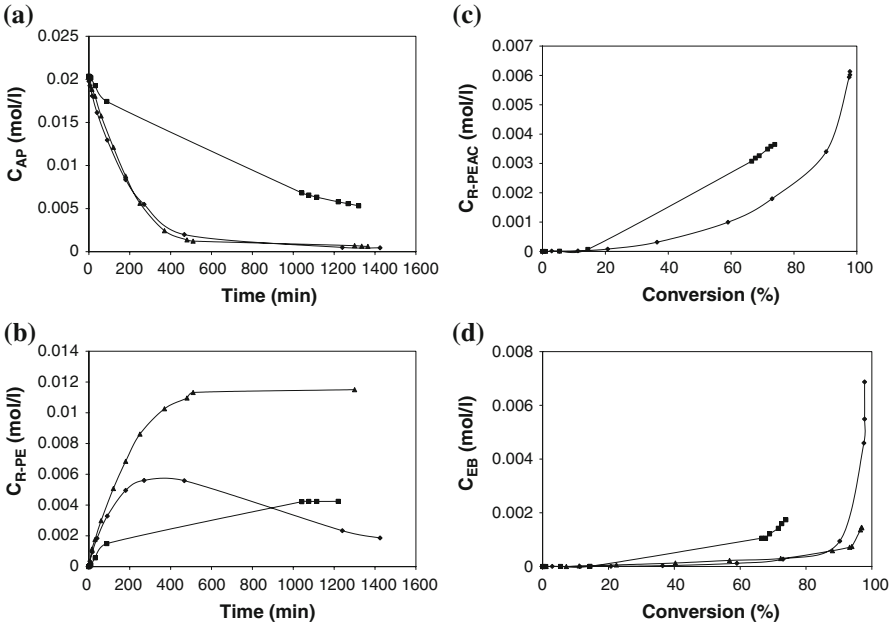

Fig. 7 Kinetics in the hydrogenation of acetophenone, **a**, and formation of *R*-1-phenylethanol, **b**, *R*-1-phenylethyl acetate, **c**, and ethylbenzene, **d**, as a function of conversion over Pd/Al_2O_3-200 and lipase (■), Pd/Al_2O_3-200–Ru/HAP (▲), and Pd/Al_2O_3-200–Ru/HAP and lipase (◆)

Table 2 Comparison of the ratio of the initial rate of formation of *R*-1-phenylethyl acetate to that of ethylbenzene, and the ratio of the initial rate of formation of (*R, S*)-1-phenylethanol to that of ethylbenzene, over different catalysts

Entry	Catalyst	$r_{R\text{-PEAC}}/r_{EB}$	$r_{(S,R)\text{-PE}}/r_{EB}$
1	Pd-100–Lip	7.0	205
2	Pd-200–Lip	3.1	12
3	Pd-200–Ru–Lip	8.3	243

Acetophenone hydrogenation, dynamic kinetic resolution of (*R,S*)-1-phenylethanol, and acylation of *R*-1-phenylethanol in one pot were demonstrated using, simultaneously, Shvo's catalyst and lipase at 70 °C in ethyl acetate (Fig. 8). The molar fraction of the *R*-1-phenylethyl acetate formed was 66% corresponding to selectivity of 74% at the conversion level of 89%. This result indicated that dynamic kinetic resolution, i.e. racemization of *S*-1-phenylethanol, happened during the reaction, because the molar fraction of *R*-1-phenylethanol was above 50%. The concentration of *R*-1-phenylethanol was close to zero during the reaction, indicating that it reacted further to *R*-1-phenylethyl acetate and no ethylbenzene was formed.

Mechanistic studies

Transformations of (R,S)-1-phenylethanol and R-1-phenylethyl acetate over different materials

Transformation of (*R,S*)-1-phenylethanol was studied over Pd/Al_2O_3 catalyst reduced at 100 °C under hydrogen or argon atmosphere (Table 3, entries 1 and 2). The main product in both cases was acetophenone, indicating that dehydrogenation of phenylethanol was the main reaction, whereas only small amounts of ethylbenzene were formed. Styrene is a product in the dehydration of phenylethanol

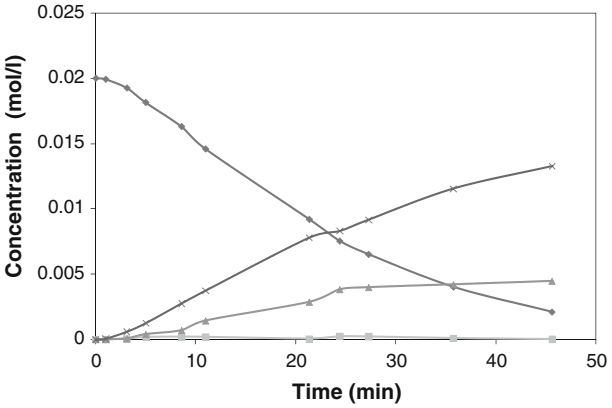

Fig. 8 Kinetics in one-pot synthesis of *R*-1-phenylethyl acetate over Shvo catalyst (0.25 g) together with lipase (0.25 g) using 0.02 mol/L initial acetophenone concentration in ethyl acetate at 70 °C. Symbols: (◆) acetophenone, (▲) *S*-1-phenylethanol, (■) *R*-1-phenylethanol, and (X) *R*-1-phenylethyl acetate

and its rapid hydrogenation to ethylbenzene over Pd/Al_2O_3 was confirmed in a separate experiment (Table 3, entry 4).

Transformations of (R,S)-1-phenylethyl acetate

The support material alumina, with a low concentration of acid sites, was inactive in debenzylation of *R*-1-phenylethyl acetate (Table 3, entry 5). Furthermore, it was not active in the dehydration of (*R,S*)-1-phenylethanol (Table 3, entry 6). Debenzylation of the desired product *R*-1-phenylethyl acetate did not occur over lipase (Table 3, entry 7). The debenzylation of *R,S*-1-phenylethyl acetate took place, however, on Pd/Al_2O_3 catalyst reduced at 100 °C (Table 3, entry 8).

Racemization of S-1-phenylethanol over different Ru catalysts

Separate racemization experiments were performed for *S*-1-phenylethanol over Ru/HAP prepared either by the impregnation method (IMP) or by ion-exchange (IE) at temperature of 70 °C or 90 °C using two different solvents, ethyl acetate and toluene, and either hydrogen or argon as gas atmosphere (Table 4). The results revealed that Ru/HAP(IMP) was inactive in the racemization of *S*-1-phenylethanol in ethyl acetate as solvent (Table 4, entries 1-3). In toluene, however, low activity was observed, but the enantiomeric excess of *S*-1-phenylethanol remained at 91% only, which is too high, because in dynamic kinetic resolution the enantiomeric excess should be close to zero. Furthermore, dehydrogenation of *S*-1-phenylethanol to acetophenone occurred over Ru/HAP(IMP) in toluene. According to the literature Ru^{3+} species are active in the racemization of *S*-1-phenylethanol forming, in the first step, a ketone which, in turn, will hydrogenate via transfer hydrogenation [13]. The results in this study, however, showed that neither Ru/HAP(IMP) nor Ru/HAP(IE) were very active in the racemization of *S*-1-phenylethanol. Ru/Al_2O_3, was a more effective racemization catalyst than Ru/HAP and promising results were achieved using only three equivalents of ethyl acetate in toluene (Table 4, entries 8–10). These results are in accordance with the literature [9], in which the catalyst

Table 3 Mechanistic studies using different intermediates and catalysts. Ethyl acetate was used as a solvent and the reaction temperature was 70 °C

Entry	Catalyst	Substrate	Pretreatment with H_2 at temperature (°C)	Atmosphere	Conversion (%)	Comment
1	Pd-100	(*R,S*)-PE	100	H_2	97	3% EB
2	Pd-100	(*R,S*)-PE	100	Ar	93	Main product AP, 6% EB, no styrene
3	Pd-100	(*R,S*)-PE	100	H_2	15	3% AP and 12% EB
4	Pd-100	Styrene	100	H_2	100	EB
5	Al_2O_3	(*R,S*)-PEAC	–	H_2	0	–
6	Al_2O_3	(*R,S*)-PE	–	Ar	0	–
7	Lipase	(*R,S*)-PEAC	–	H_2	0	–
8	Pd-100	(*R,S*)-PEAC	–	H_2	47	46% EB

was tested under conditions very close to those required for performing the desired cascade reactions in a one-pot manner.

Preliminary studies were conducted using Ru/Al_2O_3–lipase for dynamic kinetic resolution of (*R,S*)-1-phenylethanol and $PdZn/Al_2O_3$–Ru/Al_2O_3–lipase catalysts in one-pot synthesis of *R*-1-phenylethyl acetate. Because Ru/Al_2O_3 was active in the racemization experiments (see above), it was also tested in dynamic kinetic resolution of (*R,S*)-1-phenylethanol using lipase as a transesterification catalyst (Fig. 9). The results revealed that 94% conversion of *R*-1-phenylethanol was achieved within 1315 min and, furthermore, that 11% of the *S*-1-phenylethanol was converted via *R*-1-phenylethanol to *R*-1-phenylethyl acetate, indicating that dynamic kinetic resolution over this catalyst was possible.

To develop a working catalyst for one pot synthesis of *R*-1-phenylethyl acetate, bimetallic $PdZn/Al_2O_3$ was used for hydrogenation of acetophenone either together with lipase or with lipase and Ru/Al_2O_3 as a racemization catalyst. The benefit of a bimetallic catalyst is, according to the literature, that it should be more selective than a monometallic Pd catalyst and able to produce less ethylbenzene than the latter [18]. The initial reaction rate in acetophenone hydrogenation was close to the rate achieved over Pd-200, when using the same Pd-to-acetophenone ratio of 0.02. Furthermore, it can be observed from Fig. 10a that Ru/Al_2O_3 did not have any effect on the acetophenone conversion. The reason for this is that Ru is not in the metallic state (see above).

The formation rates for *R*-1-phenylethanol were also initially the same, but after prolonged reaction times *R*-1-phenylethanol reacted more rapidly over $PdZn/Al_2O_3$–Ru/Al_2O_3–lipase catalysts than over $PdZn/Al_2O_3$–lipase (Fig. 10b) and smaller amounts of the desired product were obtained over the former catalyst than when using $PdZn/Al_2O_3$–lipase catalysts (Fig. 10c). Furthermore, debenzylation of

Table 4 Kinetics for racemization of *S*-PE over Ru/HAP and over Ru/HAP(IE) using the glass reactor with a liquid phase volume of 250 mL, if not stated otherwise

Entry	Catalyst	Substrate/metal ratio	Atmosphere/solvent	Temperature (°C)	Conversion (%)	ee (%)[c]
1	Ru/HAP (IMP)[a]	112	H_2/toluene	70	Inactive	>99
2	Ru/HAP (IMP)	33	H_2/toluene	70	<4	92
3	Ru/HAP (IMP)	33	Ar/toluene	70	Inactive	99
4	Ru/HAP (IMP)	33	Ar/toluene	90	Low	91 (AP = 17%)
5	Ru/HAP (IE)	112	H_2/ethyl acetate	70	1	97
6	Ru/HAP (IE)	112	H_2/toluene	70	>8	96
7	Ru/HAP (IE)	33	Ar/toluene	90	10	97, 10% AP
8	Ru/Al_2O_3	33[b]	Ar/toluene	90	98	4.3 (AP = 62%)
9	Ru/Al_2O_3	33[b]	Ar/ethyl acetate	70	25	99 (AP = 24%)
10	Ru/Al_2O_3	33[b]	Ar/3 eq of ethyl acetate in toluene	70	45	85 (AP = 35%)

[a] Catalyst prereduced at 200 °C

[b] In 8 mL vessel, 1000 rpm stirring

[c] Acetophenone molar fraction in the parentheses

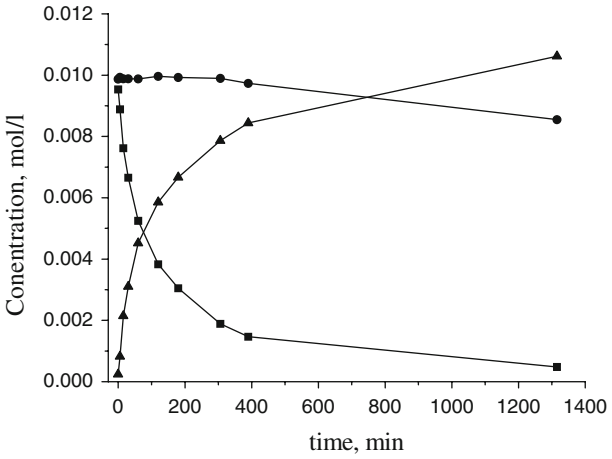

Fig. 9 Dynamic kinetic resolution of (*R,S*)-1-phenylethanol at 70 °C over 4 wt% Ru/Al_2O_3 catalyst, using 3 equivalents of ethyl acetate, in toluene as solvent. The initial concentrations of (*R,S*)-1-phenylethanol and ethyl acetate were 0.02 mol/L and 0.06 mol/L, respectively. The catalyst and lipase amounts were 100 mg and 62.5 mg, respectively. Symbols: (■) *R*-1-phenylethanol, (●) *S*-1-phenylethanol, and (▲) *R*-1-phenylethyl acetate

R-1-phenylethyl acetate occurred over the $PdZn/Al_2O_3$–lipase catalyst system, because a maximum was visible in the concentration profile of *R*-1-phenylethyl acetate (Fig. 10c). The formation of ethylbenzene was at the same level for all three catalyst systems, i.e. for Pd-200–Lip, for $PdZn/Al_2O_3$–Ru/Al_2O_3–lipase, and for $PdZn/Al_2O_3$–lipase, indicating that use of the bimetallic catalyst did not, as expected, suppress the hydrogenolysis reaction. When formation of *S*-1-phenylethanol was plotted against *R*-1-phenylethanol (Fig. 10d) it was seen that the initial formation rates for *S* and *R*-1-phenylethanol were the same, but after 30 min reaction time accumulation of *S*-1-phenylethanol in the reaction mixture was faster than that of *R*-1-phenylethanol, because *R*-1-phenylethanol reacted to the ester whereas *S*-1-phenylethanol reacted only slowly to ethylbenzene, but no racemization of it occurred. Finally the concentrations of both *R* and *S*-1-phenylethanol decreased because of formation of ethylbenzene.

As a conclusion it can be stated that these preliminary results indicated that Ru/Al_2O_3 was active in dynamic kinetic resolution of (*R,S*)-1-phenylethanol, but that one-pot synthesis using $PdZn/Al_2O_3$–Ru/Al_2O_3–lipase was not successful. The reason for this is most probably the sensitivity of the Ru/Al_2O_3 catalyst toward esters depending on their structure as stated elsewhere [8]. A detailed kinetic study starting from acetophenone hydrogenation using $PdZn/Al_2O_3$–Ru/Al_2O_3–lipase as catalyst will be the topic of a forthcoming publication.

Conclusions

Three different types of catalysts were investigated in one-pot synthesis of *R*-1-phenylethyl acetate, i.e. Pd/Al_2O_3 for hydrogenation of acetophenone, immobilized

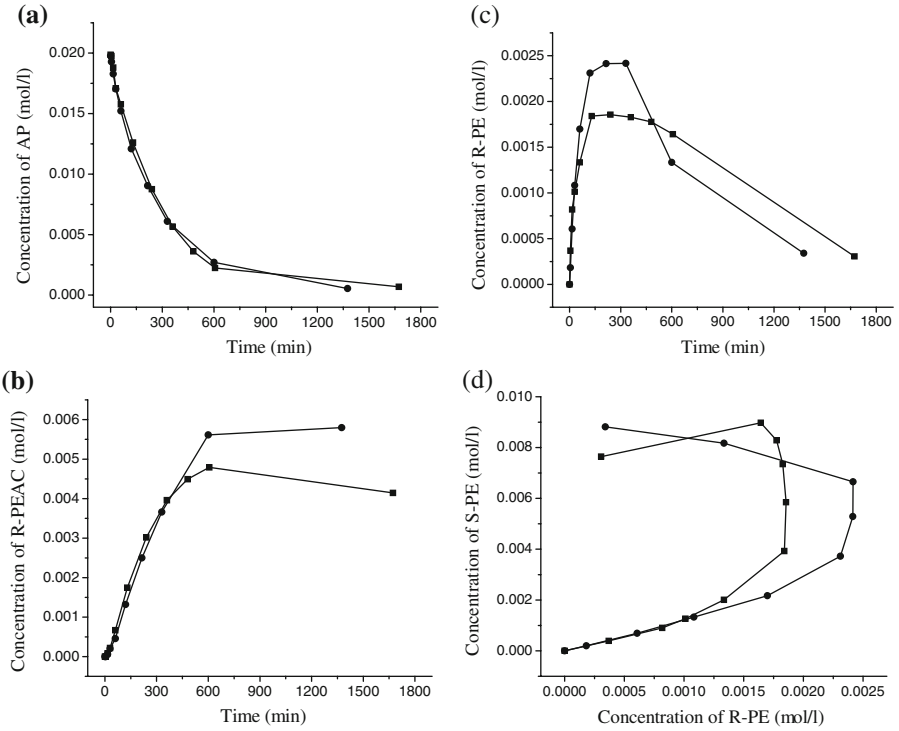

Fig. 10 Kinetics for acetophenone hydrogenation, **a**, and formation of *R*-1-phenylethanol, **b**, *R*-1-phenylethyl acetate, **c**, and formation of S-1-phenylethanol versus *R*-1-phenylethanol, **d**, over (●) PdZn/Al_2O_3 and lipase and (■) PdZn/Al_2O_3 and Ru/Al_2O_3 and lipase. The amounts of lipase, PdZn/Al_2O_3, and Ru/Al_2O_3 were 62.5, 312, and 100 mg, respectively. The initial acetophenone and ethyl acetate concentrations were 0.02 and 0.06 mol/L, respectively

lipase for kinetic resolution of *R*-1-phenylethanol, and Ru supported on hydroxyapatite for racemization of *R*-1-phenylethanol. In the hydrogenation of acetophenone the effect of the Pd/Al_2O_3 reduction temperature was investigated. Reduction at 200 °C resulted in more active catalyst than that reduced at 100 °C. The reaction was, however, the fastest over Pd/Al_2O_3 combined with Ru/HAP which were reduced at 100 °C, despite the fact that Ru hydroxyapatite alone was inactive in the hydrogenation of acetophenone. When all three catalysts, Pd/Al_2O_3, Ru/HAP, and lipase, were used as a mixture simultaneously in the system, it was observed that ethylbenzene formation was promoted in the presence of lipase. This result indicates that debenzylation of *R*-1-phenylethyl acetate is faster than dehydration of *R,S*-1-phenylethanol. As a conclusion it can be stated that the largest amounts of the desired product, *R*-1-phenylethyl acetate were achieved after prolonged reaction over the Pd/Al_2O_3–Ru/HAP–lipase catalyst system because of minor deactivation of the Pd/Al_2O_3 catalyst leading to high conversions of acetophenone and in the presence of additional sites on Ru/HAP leading to reduced debenzylation of *R*-1-phenylethyl acetate.

The main product formed from (*R,S*)-1-phenylethanol over Pd/Al_2O_3 catalyst was acetophenone, under hydrogen or argon, indicating that dehydrogenation of a

secondary alcohol was favored over this catalyst. The desired product, *R*-1-phenylethyl acetate was stable over lipase and over alumina support, but its debenzylation occurred over Pd/Al_2O_3.

In the racemization experiments Ru supported on hydroxyapatite led to acetophenone from (*R,S*)-1-phenylethanol via dehydrogenation, with racemization occurring to a minor extent only. Another racemization catalyst, Ru/Al_2O_3, was more active in racemization than Ru/HAP, giving the lowest enantiomeric excess of 91% at low conversion level in toluene. Ru/Al_2O_3 was active in dynamic kinetic resolution of (*R,S*)-1-phenylethanol, but not, however, in one-pot synthesis of *R*-1-phenylethyl acetate together with $PdZn/Al_2O_3$ and lipase catalysts. It can be tentatively concluded that the activity of the supported Ru catalysts was sufficient for one-pot synthesis of *R*-1-phenylethyl acetate including dynamic kinetic resolution. One-pot synthesis of *R*-1-phenylethyl acetate was, however, confirmed using a homogeneous Shvo's catalyst.

Acknowledgements This work is part of the activities at the Åbo Akademi Process Chemistry Centre (ÅA-PCC) within the Finnish Centre of Excellence Programme (2000–2011) appointed by the Academy of Finland. Krisztian Kordas acknowledges the Academy of Finland for funding (120853, 124357, 128626).

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