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ON MECHANISMS OF CATALYTIC REACTIONS

Mechanistic Investigations of the Reaction Network in Chemo-Bio Catalyzed Synthesis of *R*-1-Phenylethyl Acetate[1]

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Abstract—The kinetics and reaction network of the one-pot synthesis of *R*-1-phenylethyl acetate was investigated at 70°C in toluene over a combination of three different catalysts: $PdZn/Al_2O_3$ as a catalyst for acetophenone hydrogenation, lipase as an enzymatic catalyst for *R*-1-phenylethanol acylation with ethyl acetate and Ru/Al_2O_3 as a racemization catalyst for *S*-1-phenylethanol. In addition to the desired reactions, other reactions, namely hydrogenolysis and dehydration of (*R, S*)-1-phenylethanol and debenzylation of (*R, S)*-1-phenylethyl acetate also occurred. The kinetic results revealed that ethylbenzene formation was enhanced with higher amounts of $PdZn/Al_2O_3$, whereas lipase did not catalyze ethylbenzene formation. Furthermore, ethylbenzene was formed in the hydrogenolysis of (*R, S*)-phenylethanol and in the debenzylation of (*R, S*)-1-phenyl-ethylacetate over Pd/Al_2O_3 catalyst. The presence of Ru/Al_2O_3 catalyst, in which Ru was in the oxidation state of 3^+, enhanced the formation of *R*-1-phenylethyl acetate, although no clear racemization of *S*-1-phenylethanol during the one-pot synthesis of *R*-1-phenylethyl acetate was observed. Dynamic kinetic resolution of (*R, S*)-1-phenylethanol in toluene, was, however, demonstrated over Ru/Al_2O_3 and lipase.

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One-pot synthesis is an important method aiming for process intensification and at the same time for minimizing amount of waste, number of reactors and required energy and to perform several reaction steps in one-pot over different catalysts without separation and purification of the formed intermediates [1]. The combining of chemo-bio catalyzed transformations, especially hydrogenation with kinetic resolution is relatively scarcely reported in literature [1]. One-pot synthesis of *R*-1-phenylethyl acetate, involving hydrogenation of acetophenone, acylation of *R*-1-phenylethanol and racemization of *S*-1-phenylethanol has been already successfully demonstrated using a homogeneous Schvo's catalyst together with lipase [2]. The benefits to use heterogeneous catalysts in the present system would be, however, economic, since the homogeneous metal complexes are usually expensive and the catalyst separation and reuse is difficult.

One-pot synthesis of *R*-1-phenylethyl acetate was demonstrated starting from acetophenone hydrogenation using both a Pd/Al_2O_3 catalyst and a lipase in the same reactor [3]. One challenge in acetophenone hydrogenation is to avoid hydrogenolysis of the formed product, (*R, S*)-1-phenylethanol, over Pd supported catalysts. Recently a bimetallic catalyst selective in acetophenone hydrogenation giving only small amounts of ethylbenzene as a by-product was used [4]. Furthermore, there is a lack of an active and selective racemization catalysts, which could afford more than 50% yield of the desired product. Supported Ru catalysts have been reported to be active in the dynamic kinetic resolution of secondary alcohols, but racemization activity was declined in the presence of esters, which are unavoidably present in one-pot synthesis of *R*-1-phenylethyl acetate [5].

The aim in this work was to elucidate the reaction network of the one-pot synthesis of *R*-1-phenylethyl acetate in the presence of a bimetallic hydrogenation catalyst, $Pd\text{-}Zn/Al_2O_3$, an enzyme and a racemization catalyst, Ru/Al Ru/Al_2O_3 (see Scheme). The emphasis is to reveal the interrelated functions of the different catalysts.

One-pot synthesis of *R*-1-phenylethyl acetate starting from acetophenone hydrogenation.

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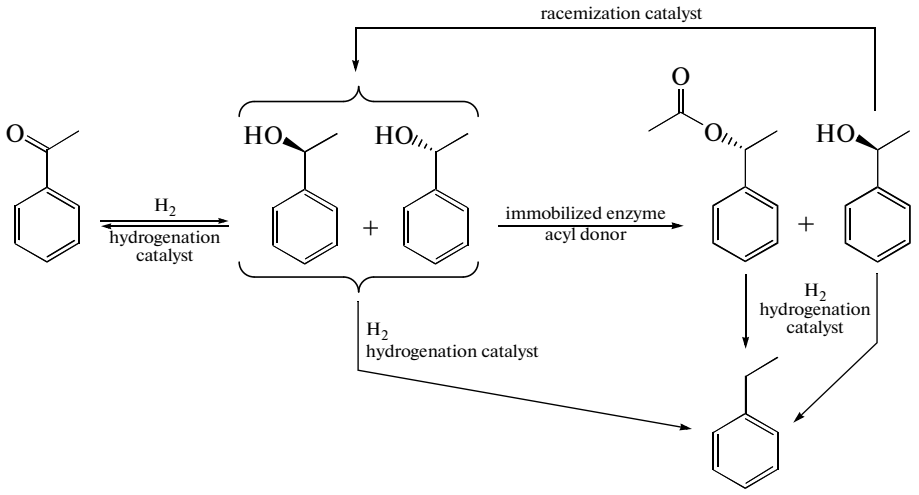

Scheme.

EXPERIMENTAL

(2 wt% Pd + 0.63 wt% Zn)/Al_2O_3 catalyst was prepared according to [6] using the metal precursors $Zn(OAc)_2 \cdot 2H_2O$ (220 mg, 1 mmol, Fluka, >99.5%) and $Pd(OAc)_2 \cdot 2H_2O$ (224 mg, 1 mmol, Sigma-Aldrich, 99.9%). The complex was confirmed to be the correct compound according to NMR ^1H (600.13 MHz, $CDCl_3$): 2.02 (s, 4OAc). The catalyst was prepared using incipient-wetness technique according to [7] as follows: the above prepared complex $PdZn(OAc)_4 \cdot H_2O$ (82.6 mg) was dissolved in absolute ethanol (3 ml) at 25°C and the solution was added dropwise to alumina (UOP, 1 g). This catalyst was pretreated in argon flow with the following temperature programme: heating with 5°C/min velocity until 80°C (120 min) and thereafter reducing by hydrogen with the same velocity until 250°C (60 min). The hydrogen then was switched to argon and this temperature was kept for 20 min with subsequent cooling to room temperature. The catalyst 4 wt % Ru/Al_2O_3 was prepared by the method described in [8] using $RuCl_3$ as a Ru source and alumina (UOP) as a support.

The transmission electron microscopy (TEM) measurements for determination of metal particle size distributions were made with LEO 912 Omega, voltage 120 kV. X-ray diffraction (XRD) measurements were made with Siemens D5000, CuK_α radiation. Nitrogen adsorption measurements of specific surface areas of the catalysts were performed with Carlo Erba (Sorptomatic 1900 Instruments). XPS spectra were recorded with Kratos Axis Ultra electron spectrometer equipped with a delay line detector. A monochromated AlK_α source operated at 150 W. The binding energy scale was referenced to the C 1s line of aliphatic carbon, set at 285.0 eV. Processing of the spectra was accomplished with the Kratos software.

The kinetic experiments were performed in a glass reactor under flowing hydrogen (AGA, 99.999%). The deoxygenated solvent (toluene) containing acetophenone (Fluka) with the initial concentration of 0.02 mol/l, an immobilized lipase (Novozym 435) (the mass in a range of 31–125 mg) and unreduced 4 wt % Ru/Al_2O_3 catalyst (100 mg) were added into the reactor containing the in-situ prereduced $Pd–Zn/Al_2O_3$ catalyst (the mass of 156–624 mg). The metal supported catalysts exhibited the particle sizes below 63 μm and the stirring rate was normally 500 rpm. The substrate to Pd molar ratio was 46.4, 23.3 and 11.6 in experiments with 156, 312, and 624 mg of Pd-Zn/Al_2O_3, respectively. Some experiments were performed using 5 wt % Pd/Al_2O_3 with alumina from UOP and 5 wt % Pd/Al_2O_3 (Degussa) as a hydrogenation catalyst. Ethyl acetate with the concentration of 0.06 mol/l was used as an acyl donor. In addition to hydrogenation, also some experiments were performed using (*R, S*)-phenylethyl acetate (Acros, >98%) and (*R, S*)-1-phenylethanol (Acros, 97%) as reactants.

The initial catalytic activity was calculated using the following equation:

$$r_{in} = \frac{\Delta n}{\Delta t m_{Pd}},$$

where n stands for molar amount of acetophenone (mmol) converted within 30 min, t is time (min) and m_{Pd} is mass of Pd (g).

The liquid phase samples were withdrawn from the reactor after certain time intervals and analyzed with a gas chromatograph containing a chiral column (Supelco Bex-Dex 225 (length 30 m, diameter 250 μm, film thickness 0.25 μm) and a flame ionization detector using the following temperature programme: 66°C (5 min)—heating 20°C/min—111°C (10 min)—heating 20°C/min—190°C.

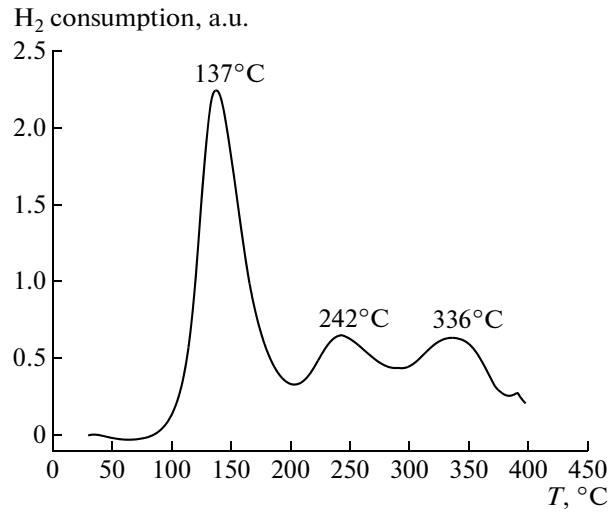

Fig. 1. Temperature-programmed reduction profile for Ru/Al_2O_3.

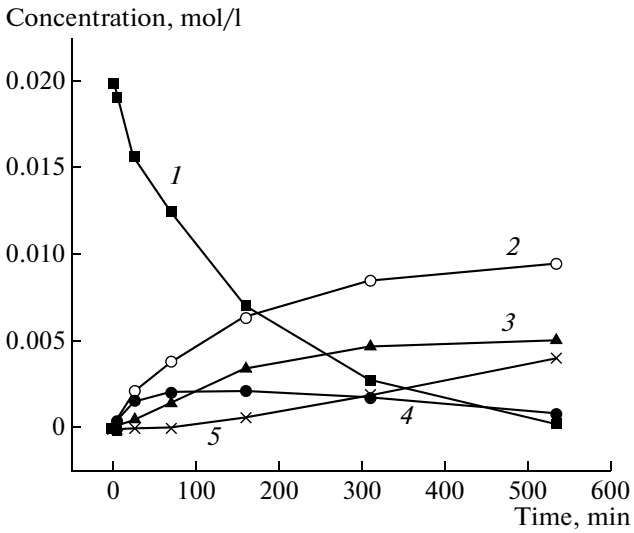

Fig. 2. Kinetics of one-pot synthesis of *R*-1-phenylethyl acetate at 70°C: *1*—acetophenone, *2*—*R*-1-phenylethanol, *3*—*S*-1-phenylethanol, *4*—*R*-1-phenylethyl acetate, *5*—ethylbenzene. Conditions: 0.02 mol/l of acetophenone, 0.06 mol/l of ethyl acetate in toluene as a solvent, 312 mg of (2 wt % Pd + 0.63 wt % Zn)/Al_2O_3, 125 mg of lipase and 100 mg of 4 wt % Ru/Al_2O_3.

RESULTS AND DISCUSSION

Alumina (UOP) used as a catalyst support exhibited low concentrations of the Brønsted and Lewis acid sites concentration (7 and 156 μmol/g_{cat}, respectively) [9]. The BET specific surface area of the support was 306 m^2/g_{cat}. The average metal particle sizes of (2 wt % Pd + 0.63 wt % Zn)/Al_2O_3 and 4 wt % Ru/Al_2O_3 according to TEM measurements were 1.3 nm in both catalysts. There were no peaks detected by XRD indicating that the metal particle sizes were below 3 nm, which is the limit for detecting metal crystallites with XRD. This result is in accordance with the TEM results. XPS results for Pd-Zn/Al_2O_3 catalyst revealed that the binding energies for Pd $3d_{5/2}$ and for Pd $3d_{3/2}$ region varied from 334.3 to 335.5 eV and from 339.6 to 340.8 eV, respectively, whereas for metallic Pd the binding energy of 335.0 eV has been reported in literature [10] thus suggesting that in the current work Pd is in any case partially in metallic form. The peak broadness for metallic palladium should be, however, 1.50 eV, whereas in this case the peaks are broader (2.4 eV) suggesting Pd-Zn alloy formation [11].

Ru/Al_2O_3 was used under argon or under hydrogen in the racemization of (*R, S*)-1-phenylethanol and thereafter the spent catalysts were investigated using XPS. The spectra of these two catalysts showed that Ru $3p_{3/2}$ and Ru $3p_{1/2}$ were in the range of 462.3–462.6 and 484.5–484.8 eV, respectively. According to the literature the binding energies for Ru $3p_{3/2}$ and Ru $3p_{1/2}$ corresponding to Ru(III) are 462.9 and 484.8 eV, respectively [12], which is consistent with present data. Temperature-programmed reduction profile for Ru/Al_2O_3 is shown on Fig. 1. The first peak can be attributed to reduction of Ru, whereas the other two peaks can be assigned to changes occurred in the support morphology.

The kinetics of acetophenone hydrogenation was studied by performing preliminary experiments showing the absence of external mass transfer limitations, i.e., using different amounts of hydrogenation catalysts and small catalyst particles. A typical reaction kinetics from one-pot synthesis of *R*-1-phenylethyl acetate, in which acetophenone was hydrogenated within 535 min to 99% conversion, is shown in Fig. 2. As primary products, both *S*- and *R*-1-phenylethanol were formed as racemates. Thereafter, *R*-1-phenylethanol is acylated to *R*-1-phenylethyl acetate, with a very low initial rate, since the latter compound was detected only after 25 min of reaction. After 535 min of reaction the selectivity to *R*-1-phenylethyl acetate was 26% at the conversion level of 99%.

From the concentration profile of *S*-1-phenylethanol it cannot be clearly stated, whether minor racemization occurred or not under these reaction conditions over Ru/Al_2O_3, since the concentration of *S*-1-phenylethanol did not decrease during the course of the reaction. Dynamic kinetic resolution of (*R, S*)-1-phenylethanol was, however, possible over this catalyst in toluene at 70°C in the presence of three equivalents of ethyl acetate: 11% of inactive isomer *S*-phenylethanol was converted to *R*-1-phenylethyl acetate via racemization and further resolution reaction. Therefore, the final concentration of target *R*-1-phenylethyl acetate (0.0105 mol/l) exceeded the value expected from only kinetic resolution (0.094 mol/l) by 11% at 94% conversion of initial *R*-1-phenylethanol as demon-

Table 1. Kinetic results of one-pot synthesis of *R*-1-PEAc starting from acetophenone hydrogenation in dependence of amounts of Pd/Al_2O_3 and lipase

Entry	Mass of Pd/Al_2O_3, mg	Mass of lipase, mg	r_{in}, mmol min^{-1} g_{Pd}^{-1}	Conversion after 360 min, %	Selectivity to *R*-PEAc, %		Selectivity to ethylbenzene, %	
					at 50% conversion	at 90% conversion	at 50% conversion	at 90% conversion
1	156	62.5	2.8	70	26	–	3	–
2	312	62.5	2.8	91	18	26	3	14
3	624	62.5	3.2	95	10	18	4	23
4	624	125	3.0	92	10	25	20	22
5	312	31	2.4	84	16	19	7	19
6	312	125	3.2	90	24	27	2	14

Note: Initial concentration of acetophenone 0.02 mol/l, 70°C, solvent toluene, 3 equivalents of ethyl acetate as an acyl donor over (2 wt % Pd + 0.63 wt % Zn)/Al_2O_3. The amount of racemization catalyst 4 wt % Ru/Al_2O_3 was 100 mg.

strated in [13]. The active species of ruthenium was Ru(III), since Ru was not reduced under reaction conditions, as revealed from TPR (Ru is reduced at 137°C, which is much higher than reaction temperature). *S*-1-phenylethanol reacted further principally in several ways, i.e., via dehydration, and racemization. In a separate experiment over a monometallic Pd/Al_2O_3 catalyst in the presence of hydrogen it was shown that even hydrogenolysis of secondary alcohols produced ethylbenzene. Additionally Pd/Al_2O_3 catalyzed debenzylation of (*R, S*)-1-phenylethanol forming ethylbenzene was confirmed.

Ethylbenzene was formed, as explained above, via several reactions, namely debenzylation of an ester, dehydration or hydrogenolysis of secondary alcohols. The initial rate of ethylbenzene formation was only 22% of the rate achieved after 160 min reaction time. This result indicated that ethylbenzene formation was enhanced with increasing reaction time, when more primary and secondary products were formed.

Kinetics of the one-pot synthesis of *R*-1-phenylethyl acetate was systematically investigated by varying the amounts of the hydrogenation and the acylation catalysts (Table 1). The initial hydrogenation activities were calculated as moles of converted acetophenone per amount of Pd, since the hydrogenation activity of zinc was very minor (see below), and Ru was in the oxidation state 3^+ not effective in hydrogenation. When the amounts of the hydrogenation catalyst increased (Table 1, entries 1–3), the r_{in} slightly increased. When the ratio between Pd and lipase increased, higher hydrogenation rates were achieved. This result is in accordance with the earlier data [14], showing that the hydrogenation rate was slightly higher in the absence of lipase compared to its presence. The conversion of acetophenone increased, as expected, after prolonged reaction times when using larger amounts of $PdZn/Al_2O_3$ catalyst. The lowest conversion after 360 min was achieved with the Pd/lipase ratio of 2.5 being only 70%, whereas with higher ratios, namely 5 and 10, the difference in the conversion levels was not large. Thus it can be concluded that in order to achieve high conversions an excess of a hydrogenation catalyst should be used.

The formation of *R*- and *S*-1-phenylethanol was racemic with equal amounts of both alcohols. When increasing the amount of the hydrogenation catalyst, higher concentrations of *R*-1-phenylethanol were achieved, as expected. Furthermore, a maximum concentration was achieved for *R*-1-phenylethanol after 210, 175, and 70 min corresponding to the amounts of Pd-Zn/Al_2O_3 catalyst 156, 312, and 624 mg, respectively. These maximum concentrations were 0.0020, 0.0023, and 0.0034 mol/l, respectively. The concentration profiles for *R*-1-phenylethanol using 156 and 312 mg of Pd-Zn/Al_2O_3 catalyst were monotonically increasing with time, whereas a maximum in *S*-1-phenylethanol concentration was achieved using 624 mg of this catalyst. This result indicated that the formation rate of *S*-1-phenylethanol was higher than its consumption rate and thus racemization and dehydration or hydrogenolysis rates of *S*-1-phenylethanol were relatively small with lower amounts of Pd-Zn/Al_2O_3. When 624 mg of $PdZn/Al_2O_3$ catalyst was used in one-pot synthesis of *R*-1-phenylethyl acetate, also the formation of ethylbenzene was enhanced thus giving as a result a maximum concentration of *S*-1-phenylethanol after 442 min.

The formation rates of the desired product, *R*-1-phenylethyl acetate (*R*-PEAc), increased with decreasing amount of the hydrogenation catalyst from 624 to 312 and further to 156 mg (Fig. 3a). At the same time the selectivities to *R*-1-phenylethyl acetate increased with decreasing amount of $PdZn/Al_2O_3$ (Table 1, entries 1–3). At higher amounts of the hydrogenation catalyst (624 mg) the ethylbenzene for-

mation was enhanced, especially from secondary alcohols, thus lowering the yield of *R*-1-phenylethyl acetate. A maximum of the concentration of *R*-1-phenylethyl acetate was achieved after 285 min reaction time, thereafter ester debenzylation was observed. When *R*-1-phenylethyl acetate concentration was plotted as a function of acetophenone conversion (Fig. 3a), it can be clearly seen that ester formation is a consecutive reaction.

Ethylbenzene formation was extensively enhanced with a large amount of $PdZn/Al_2O_3$ catalyst (Table 1). After 400 min of reaction time the selectivity to ethylbenzene with 624 mg of $Pd\text{-}Zn/Al_2O_3$ was 46% at the conversion level of 97%. In order to understand a role of active metal and support in this reaction, an additional experiment was performed using (*R, S*)-1-phenylethanol as a reactant over Al_2O_3 powder. The result was the absence of any transformation of secondary alcohol at 70°C in ethylacetate as a solvent. Thus, it can be concluded that the formation of ethylbenzene was catalyzed by Pd.

In the second series (Fig. 3b), when the amounts of the hydrogenation catalyst and the racemization catalyst were kept constant, namely 312 and 100 mg, respectively, the lipase amount was varied being 31, 62.5, and 125 mg (Table 1, entries 5, 2, and 6) with increasing amount of lipase. The initial hydrogenation rates were very close to each other, as expected. Slightly lower conversion of acetophenone was achieved with lower amount of lipase, being, however, within the reproducibility limits. From the mechanistic point of view the hydrogenation rate should not be affected by the presence of enzyme.

As expected, the product distribution related to acylation was very prominently affected by the amount of lipase. Different maxima in the concentration for *R*-1-phenylethanol were achieved as a function time with different amounts of lipase (31, 62.5, and 125 mg). The corresponding maximum concentrations were 0.0027, 0.0023, and 0.0021 mol/l, respectively.

Thereafter *R*-1-phenylethanol reacted further, either to ester or to ethyl benzene.

The concentration profiles for *S*-1-phenylethanol increased with increasing time with all three amounts of lipase, since the ethylbenzene formation was not catalyzed very effectively. Furthermore, the racemization rate, which cannot be separated from the kinetic data due to the formation of ethylbenzene, could not be, however, very significant, since *S*-1-phenylethanol production was larger during the reaction than its further reaction to either *R*-1-phenylethanol or ethylbenzene.

The formation of the desired product, *R*-1-phenylethanol, was a consecutive reaction, which could be seen from the shapes of its concentration profiles (Fig. 3b). The lowest concentration of *R*-1-phenylethyl acetate was achieved, as expected, using the lowest amount of lipase, i.e., 31 mg. The selectivities to *R*-1-phenylethyl acetate increased also with increasing lipase amounts (Table 1, entries 5, 2, and 6), while the opposite was shown for ethylbenzene. Its formation decreased with increasing amount of lipase, when the amounts of the hydrogenation catalyst and the racemization catalyst were constant (Table 1, entries 5, 2, and 6). Thus, it can be concluded that there is an interrelation between the two catalysts, namely between the hydrogenation catalyst and the enzyme, since the ethylbenzene formation, which is catalyzed by Pd (hydrogenolysis or dehydration of a secondary alcohol and debenzylation of the desired product), was enhanced with a smaller amount of lipase. The catalytic effect of Pd in debenzylation is thus more prominent in the presence of only small lipase amounts. At

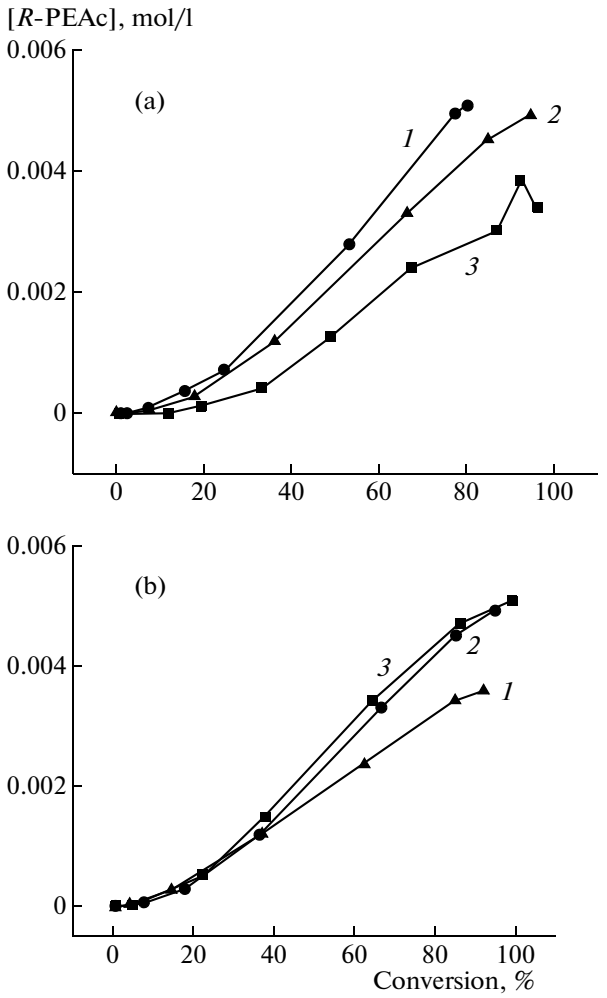

Fig. 3. Formation of *R*-1-phenylethyl acetate as a function of acetophenone conversion at initial concentration of acetophenone 0.02 mol/l, 70°C, solvent toluene, 3 equivalents of ethyl acetate as an acyl donor. (a) 100 mg of 4 wt % Ru/Al_2O_3 and 62.5 mg of lipase together with (*1*) 156, (*2*) 312, and (*3*) 624 mg of $Pd\text{-}Zn/Al_2O_3$. (b) 312 mg of $Pd\text{-}Zn/Al_2O_3$ and 100 mg of Ru/Al_2O_3 together with (*1*) 31, (*2*) 62, and (*3*) 125 mg of lipase.

Table 2. Kinetic results of one-pot synthesis of *R*-1-PEAc starting from acetophenone hydrogenation in the absence and in the presence of the racemization catalyst 4 wt % Ru/Al_2O_3

Mass of Ru/Al_2O_3, mg	r_{in}, mmol min^{-1} g_{Pd}^{-1}	Conversion after 360 min, %	Selectivity to *R*-PEAc, %		Selectivity to ethylbenzene, %	
			at 50% conversion	at 85% conversion	at 50% conversion	at 85% conversion
0	3	89	16	24	10	6
100	2.6	85	21	31	10	6

Note: Initial concentration of acetophenone 0.02 mol/l, 70°C, solvent toluene, 3 equivalents of ethyl acetate as an acyl donor over 5 wt % Pd/Al_2O_3, 127 mg of the hydrogenation catalyst together with 62.5 mg lipase.

the same time the concentration of *R*-1-phenylethyl acetate decreased.

The effect of the racemization catalyst, Ru/Al_2O_3, was investigated using 5 wt % Pd/Al_2O_3 as a hydrogenation catalyst together with lipase for acylation. Two experiments were performed in one-pot synthesis of *R*-1-phenylethyl acetate starting from acetophenone hydrogenation, in the absence and in the presence of Ru/Al_2O_3 in toluene with three equivalents of ethylacetate as an acyl donor at 70°C (Table 2). The results showed that the hydrogenation rates were close to each other indicating that Ru/Al_2O_3 is not active in the hydrogenation, as expected, since it is in the oxidation state of 3^+ and is not reduced during the reaction. The highest concentrations of both *R*- and *S*-1-phenylethanol were achieved over the catalytic system containing no racemization catalyst. Ethylbenzene formation was the same in the presence and in the absence of Ru catalyst, but a positive effect of the racemization catalyst was observed in the presence of Ru/Al_2O_3: about 24% higher selectivity to the desired product was achieved at 50% conversion of acetophenone. Since the concentration profiles for *S*-1-phenylethanol showed no decreasing trend as a function of time, it is difficult to determine the efficiency of *S*-1-phenylethanol racemization. Furthermore, it was stated [5] that esters inhibit Ru activity as a racemization catalysts and their presence in this one-pot synthesis, cannot be avoided.

In the hydrogenation of acetophenone, the effect of zinc on the formation of ethylbenzene was investigated. 5 wt % Zn/Al_2O_3 exhibited minor activity in acetophenone hydrogenation. One-pot experiments with either 5 wt % Pd/Al_2O_3 or (2 wt % Pd + 0.63 wt % Zn)/Al_2O_3 and the same Pd/acetophenone ratio showed that the hydrogenation rates and the formation of *R*-1-phenylethyl acetate were the same. The only difference was a slightly higher amount of ethylbenzene over the bimetallic catalyst. The selectivities to ethylbenzene over mono- and bimetallic catalysts were 5 and 11%, respectively, at 80% conversion of acetophenone. It should, however, be stated that the role of zinc cannot be clearly separated in these two experiments, since the alumina support in Pd/Al_2O_3 was other than in the bimetallic catalyst.

Thus, the reaction network in one-pot synthesis of *R*-1-phenylethyl acetate was investigated using $PdZn/Al_2O_3$ as a hydrogenation catalyst, a lipase as an acylation catalyst and Ru/Al_2O_3 as a racemization catalyst. Besides the desired *R*-1-phenyethylacetate, also ethylbenzene was formed via hydrogenolysis of (*R, S*)-1-phenylethanol as well as through debenzylation of (*R, S*)-1-phenylethyl acetate. Racemization of *S*-1-phenylethanol in one-pot synthesis was not prominent in the presence of esters, i.e., an acyl donor itself and the desired product, *R*-1-phenylethyl acetate, although dynamic kinetic resolution of (*R, S*)-1-phenylethanol over Ru/Al_2O_3 and lipase in toluene, was successfully demonstrated. The presence of Ru/Al_2O_3 together with $PdZn/Al_2O_3$ and lipase exhibited a positive effect on the formation of *R*-1-phenylethyl acetate compared with the absence of the racemization catalyst.

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