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Chemo-Bio Catalyzed Synthesis of *R*-1-Phenylethyl Acetate over Bimetallic PdZn Catalysts, Lipase, and Ru/Al_2O_3. Part II[1]

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Abstract—One-pot synthesis of *R*-1-phenyethylacetate at 70°C was investigated using three different catalysts simultaneously, namely a bimetallic $PdZn/Al_2O_3$ as a hydrogenation catalyst, an immobilized lipase as an acylation catalyst and Ru/Al_2O_3 as a racemization catalyst. The most active bimetallic catalyst was $PdZn/Al_2O_3$ calcined at 300°C and reduced at 400°C, whereas the most selective although less active catalyst was the one being calcined and reduced at 500°C. The highest selectivity to *R*-1-phenylethyl acetate over this catalyst was 32 at 48% conversion. Ru/Al_2O_3 was confirmed to have a positive effect on the formation of the desired product, although it was not very active in the racemization during one-pot synthesis.

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Cascade catalysis is of interest in organic synthesis both due to high environmental demands aiming at waste minimization and increasing overall process efficiency. The E-factor indicating the amount of waste per product amount is very high, especially for fine chemicals [1]. As for process intensification there are several tools to achieve it via for example enhancing heat and mass transfer by applying ultrasound, microwaves, etc. An alternative approach to process intensification is one-pot synthesis, in which the underlying idea is to combine two or several different catalysts and reaction steps in a single apparatus [2]. Already a number of examples is taking advantage of chemo-bio and chemo-chemo catalysts in one reactor unit [3]. There are, however, very few reports that introduce e.g., a hydrogenation coupled to an enzymatic reaction, especially when the hydrogenation catalyst is a heterogeneous supported metal one. Although several successful examples could be found for homogeneous catalytic-enzymatic combinations [4], it should be noted, that homogeneous hydrogenation catalysts are often very expensive exotic organometallic complexes. In dynamic kinetic resolution, studied especially by Bäckvall et al. [5], transition metal catalysts were used as additional catalysts for racemization of the undesired enantiomer resulting in molar fractions close to 100% of the desired enantiomer. The reuse of homogeneous catalysts is challenging and, thus, heterogeneous catalysts compatible with enzymatic catalysts could be an industrially more attractive solution. Heterogeneous catalysts can often be relatively cheap and robust.

The model reaction in the current study introduce illustrates one-pot synthesis of *R*-1-phenylethylacetate (*R*-1-PEAc) starting from acetophenone (see Scheme). In this system, several reactions are combined in one-pot, such as hydrogenation of acetophenone, acylation of the formed *R*-1-phenylethanol (*R*-1-PE) and racemization of *S*-1-phenylethanol (*S*-1-PE). The latter reaction allows dynamic kinetic resolution, i.e., the *S*-enantiomer is racemized during the reaction. This facilitates formation of *R*-1-PEAc in higher than 50% yields, since *S*-enantiomer is transformed to *R*-1-enantiomer and can, consequently, be acylated in the following reaction sequel.

One-pot synthesis of *R*-1-PEAc has been demonstrated in the previous publications [6, 7], when only a monometallic supported Pd catalyst was applied for acetophenone hydrogenation followed by lipase catalyzed acylation of the *R*-1-PE. The highest yield of the desired product—*R*-1-phenylethylacetate—was about 22%, at a conversion level of 46% [6]. In addi-

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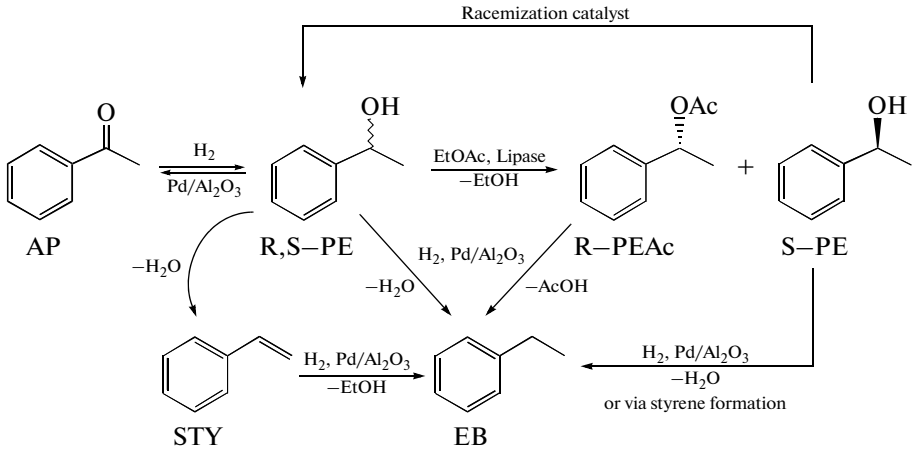

Scheme. One-pot synthesis of R-1-phenylethylacetate.

tion to hydrogenation and acylation reactions, a side-reaction leading to the formation of ethylbenzene was quite prominent [6]. Ethylbenzene (EB) can be formed over Pd metal via debenzylation of the desired ester. One possibility to decreased the EB formation would be to use a bimetallic PdZn catalyst for acetophenone hydrogenation. A similar catalyst was reported in [8] giving less ethylbenzene than a monometallic Pd/C catalyst.

Racemization of the unreacting enantiomer is typically performed over a Ru/Al_2O_3 catalyst, in which Ru exists in the oxide form [9, 10].

The aim in the current work was to study the catalytic activity and selectivity of a bimetallic $PdZn/Al_2O_3$ catalyst, together with a lipase as an acylation catalyst and with Ru/Al_2O_3 as a racemization catalyst for *S*-1-PE. The synthesis and characterization of a bimetallic $PdZn/Al_2O_3$ and Ru/Al_2O_3 were reported in Part I [10]. The industrially important product is *R*-1-PE, which is usually easily produced via hydrolyzing *R*-1-PEAc in sodium hydroxide [11].

EXPERIMENTAL

Kinetic experiments were performed in a standard laboratory scale glass reactor. Acetophenone was used as the reactant and its initial concentration was 0.02 mol/l in toluene. The liquid phase volume was 125 ml. Ethyl acetate (0.06 mol/l) was used as an acyl donor in toluene solvent. Acetophenone hydrogenation was performed at 70°C over $PdZn/Al_2O_3$ as the hydrogenation catalyst, an immobilized lipase (Novozym 435) as the acylation catalyst and Ru/Al_2O_3 as the racemization catalyst. After prereduction, catalysts were kept under toluene in order to avoid oxidation. In a typical experiment, hydrogenation was performed under an atmospheric flow of hydrogen (300 ml/min) and 312 mg of the $PdZn/Al_2O_3$ together with 62.5 mg lipase and 100 mg Ru/Al_2O_3 catalysts were mixed. The experiments were performed under kinetic regime using the stirring rate of 500 rpm. Furthermore, the particle size fraction of all supported metal catalysts was below 63 μm to suppress internal diffusion.

One-pot synthesis of *R*-1-PEAc starting from acetophenone hydrogenation*

Entry	Calcination temperature, °C	Reduction temperature, °C	Initial rate, mmol min^{-1} g_{Pd}^{-1}	Conversion after 360 min, %	Selectivity to *R*-PEAc, %		Selectivity to EB, %	
					at 50% conversion	at 90% conversionat	at 50% conversion	at 90% conversionat
1	300	400	2.7	90	25	33	0	6
2	500	400	1.5	75	25	–	4	–
3	500	500	1.6	48	32	–	3	–

* Catalysts: (2 wt % Pd + 5 wt % Zn)/Al_2O_3 (315 mg), 4 wt % Ru/Al_2O_3 (100 mg), lipase (62.5 mg). Conditions: initial concentration of acetophenone 0.02 mol/l, 70°C, solvent toluene, 3 equivalents of ethyl acetate as an acyl donor.

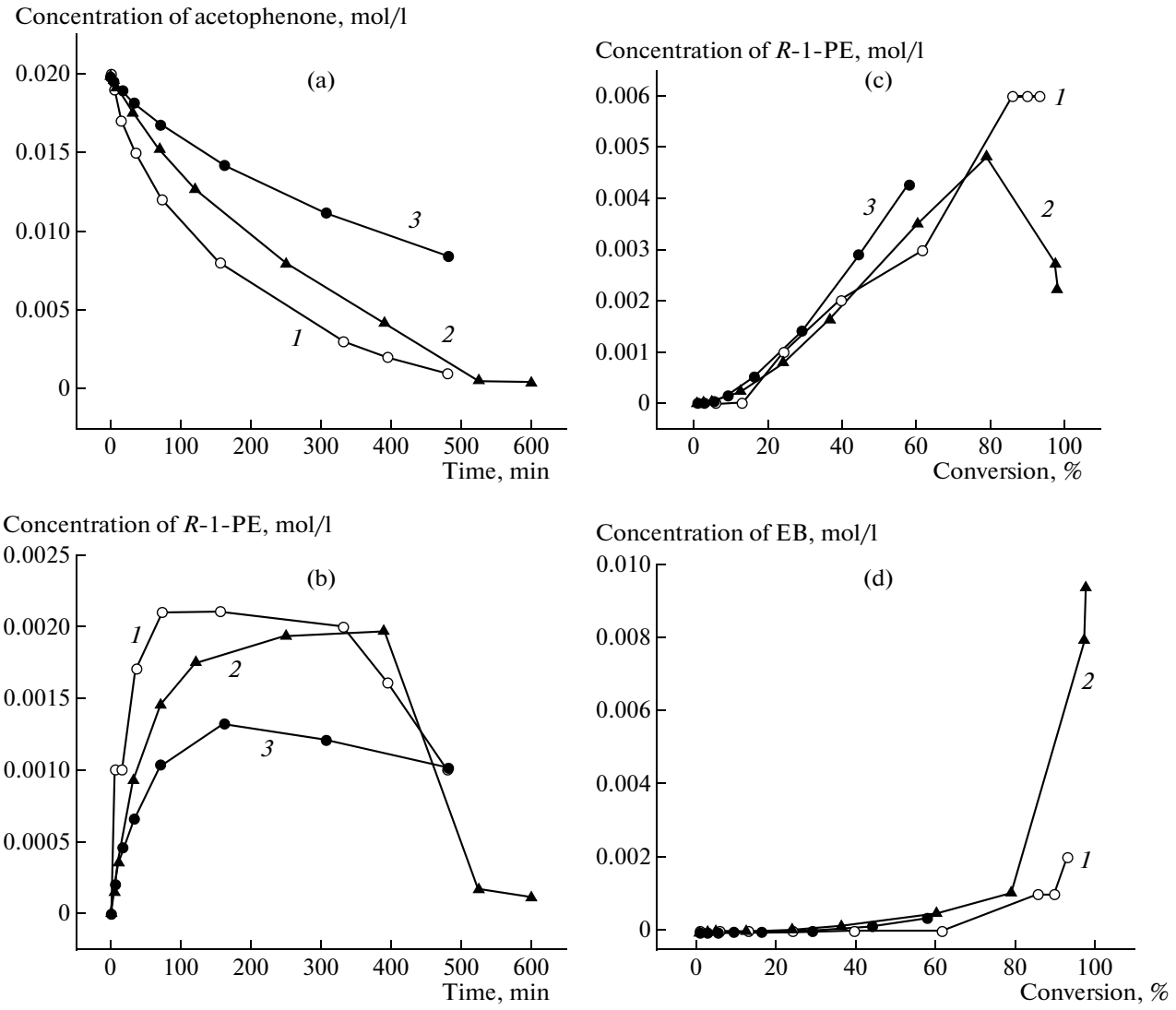

Fig. 1. Kinetics of acetophenone hydrogenation (a) and *R*-1-PE formation (b), also formation of *R*-1-PEAc (c) and ethylacetate (d) as functions of conversion in one-pot synthesis at 70°C on the samples: *1*—PdZn-300-400, *2*—PdZn-500-400, *3*—PdZn-500-500. Initial concentrations of acetophenone and ethylacetate 0.02 and 0.06 mol/l, respectively. The amounts of catalysts: $PdZn/Al_2O_3$—312 mg, lipase—62.5 mg, 4 wt % Ru/Al_2O_3—100 mg.

RESULTS AND DISCUSSION

The effects of catalyst calcination and reduction temperatures were evaluated using (2 wt % Pd + 5 wt % Zn)/Al_2O_3 as the hydrogenation catalyst, lipase as the acylation catalyst and 4 wt % Ru/Al_2O_3 as the racemization catalyst. The reactions were performed at 70°C, in toluene (0.02 and 0.06 mol/l of acetophenone and ethyl acetate, respectively).

The highest initial hydrogenation rate was achieved over the catalyst calcined at 300°C and reduced at 400°C (table), whereas lower initial activities were observed for the catalysts calcined at 500°C and reduced thereafter either at 400 or at 500°C. These results can be explained by the fact that large Pd particles were also detected in the cases, when the catalysts were calcined at 500°C [10]. Thus, it is preferable to use a catalyst which has been calcined at 300°C. Furthermore, the most active catalyst exhibited the highest surface concentrations of Pd and Zn [10], confirmed by XPS results.

Large differences were observed in the acetophenone conversion after 360 min for the three different $PdZn/Al_2O_3$ catalysts. Consequently, the conversion levels were decreased in row PdZn-300-400 ≫ PdZn-500-400 ≫ PdZn-500-500 indicating that high catalyst reduction temperatures (500°C) should be avoided (table, Fig. 1a), as it easily leads to slight sintering of metal particles as confirmed by TEM [10]. The more low reaction rates were observed after 30 min for the catalyst both calcined and reduced at 500°C (only 48% conversion of acetophenone after 360 min).

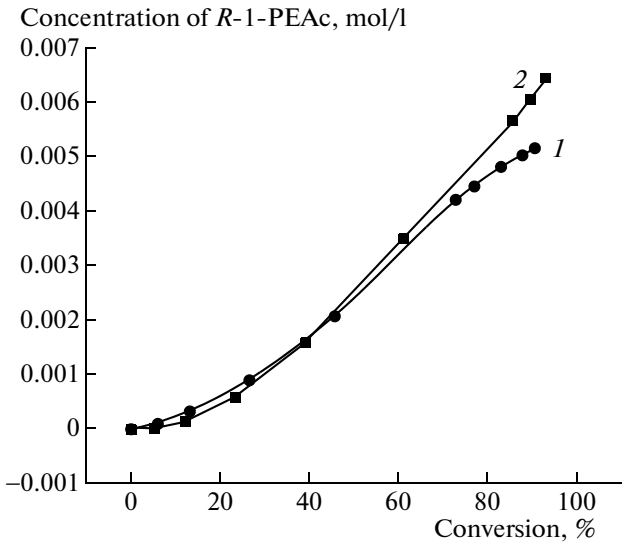

Fig. 2. Formation of *R*-1-PEAc as a function of acetophenone conversion in the absence (*1*) and in the presence (*2*) of Ru/Al_2O_3 catalyst. Conditions of reaction: temperature 70°C, solvent toluene, initial concentrations of acetophenone and ethylacetate 0.02 and 0.06 mol/l, respectively. The amounts of the catalysts: PdZn-300-400—312 mg, lipase—62.5 mg, 4 wt % Ru/Al_2O_3—100 mg.

The product distribution obtained over different $PdZn/Al_2O_3$ catalysts varied very much depending on the pretreatment conditions (Fig. 1, table). The highest concentration of the intermediate product—*R*-1-phenylethanol—was achieved for the most active catalyst, i.e., the one calcined at 300°C and reduced at 400°C. Furthermore, the *R*-1-PE yield decreased in line with the trend observed in the catalyst activities and conversions. Consequently, the catalyst calcined at 300°C and reduced at 400°C exhibited the highest activity towards *R*-1-PE. For all three catalysts, maxima in the *R*-1-PE concentration as a function of time were observed (Fig. 1b).

In contrast to the kinetic curves observed for *R*-1-PE, no maxima were observed for *S*-1-PE over different PdZn catalysts as a function of time. The yield of *S*-1-PE increased with increasing time indicating that two *S*-1-PE transformation reactions, namely racemization and hydrogenolysis, were not very prominent since the rate of *S*-1-PE formation was always higher than its consumption rate in the consecutive reactions. Racemization of *S*-1-PE has been confirmed in a separate experiment in toluene, at 70°C, over Ru/Al_2O_3. The contribution from the racemization of *S*-1-PE cannot be precisely quantified, but the effect is not very significant. It has been stated in [12] that the racemization of *S*-1-PE was inhibited by the presence of esters. In the current case ethylacetate used as an acyl donor, moreover, the desired product—*R*-1-PEAc—is also an ester. Thus, this could lead to deactivation of Ru/Al_2O_3 catalyst.

The formation of the desired ester product—*R*-1-PEAc—was compared at the same conversion levels (Fig. 1c). It was seen that the highest concentrations of it were achieved over the catalyst calcined at 500°C and reduced at 500°C. The challenge associated with this catalyst was, however, its low activity. The best performance was observed over the catalyst PdZn-300-400, giving the yield of *R*-1-PEAc of 30%. Furthermore, the enantiomeric excess of *R*-1-PEAc was 100%. For the catalyst PdZn-500-400, the consecutive debenzylation reaction occurred very prominently after 80% conversion (Fig. 1c). Debenzylation is known to be catalyzed especially by Pd. XPS analysis in line showed that the fraction of the metallic Pd(0) for the most selective catalyst (PdZn-300-400) was the lowest, namely 40% [10]. On the other hand, the least selective catalyst (PdZn-500-400 active due to presence of not too large metal particles) displayed a high fraction of Pd(0) (46%) [10], a value larger than that for PdZn-300-400. Furthermore, for the catalyst exhibiting low activity, namely PdZn-500-500, the high fraction of metallic Pd was not very effective because of large metal particles size.

The behavior of the racemization catalyst—Ru/Al_2O_3—was investigated by performing two comparative experiments in the one-pot synthesis of *R*-1-PEAc over the most active hydrogenation catalyst PdZn-300-400 and lipase both in the presence and in the absence of the racemization catalyst. The hydrogenation rates were identical in both cases as expected, since Ru is in higher oxidation state known to be not active in the hydrogenation.

The presence of the racemization catalyst promoted the formation of *R*-1-PEAc. At 90% conversion level, the concentration of the product, *R*-1-PEAc, was 0.0058 mol/l, whereas only 0.0047 mol/l was achieved in the absence of the Ru/Al_2O_3 (Fig. 2). Concentration of *S*-1-PE as a function of time, was, however, monotonously increasing with increasing conversion as stated above and no clear racemization or hydrogenolysis of it could be observed. In any case more *R*-1-PEAc was formed in the presence of racemization catalyst.

Thus, one-pot synthesis of *R*-1-phenylethylacetate was investigated over three different heterogeneous catalysts being present in the reactor simultaneously, namely a bimetallic $PdZn/Al_2O_3$ for hydrogenation, an immobilized lipase for acylation and Ru/Al_2O_3 for racemization of the undesired *S*-1-phenylethanol. The experiments were performed at 70°C, in toluene as the solvent, using 3 equivalents of ethylacetate as the acyl donor.

The effect of calcinations and reduction temperature of $PdZn/Al_2O_3$ catalysts on one-pot synthesis of *R*-1-PEAc was investigated too. The most active catalyst was one calcined at 300°C and reduced at 400°C due to slightly smaller metal particles compared to the two other catalysts. This catalyst exhibited the highest surface concentration of Pd and Zn according to XPS

analysis. The highest yield of the desired product—*R*-1-PEAc—was 30 at 90% conversion of acetophenone over the $PdZn/Al_2O_3$ catalyst, calcined at 300°C and reduced at 400°C. The enantiomeric excess of *R*-1-PEAc was 100%.

The yield of *R*-1-PE was highest over the most active catalyst calcined at 300°C and reduced at 400°C. After longer reaction time, *R*-1-PE reacted to *R*-1-PEAc and partially to ethylbenzene via hydrogenolysis. The extent of racemization of *S*-1-PE was quite minor due to the fact that alcohols and esters inhibit the racemization reaction. When comparative experiments in one-pot synthesis of *R*-1-PEAc, both in the presence and in the absence of Ru/Al_2O_3, were performed, it was found that 19% higher concentration of *R*-1-phenyethylacetate was achieved in the presence of Ru/Al_2O_3. This result indicated that Ru/Al_2O_3 exhibited a positive overall effect on the one-pot synthesis of *R*-1-PE.

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