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One-pot utilization of heterogeneous and enzymatic catalysis: Synthesis of *R*-1-phenylethyl acetate from acetophenone

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ABSTRACT

One-pot synthesis of *R*-1-phenylethyl acetate was investigated starting from hydrogenation of acetophenone over a metal-supported catalyst followed by acylation of the formed *R*-1-phenylethanol over an immobilized lipase. The most promising catalyst for the hydrogenation step was Pd/Al_2O_3, which in combination with an immobilized lipase yielded maximally 22% *R*-1-phenylethyl acetate. The support acidity had a crucial effect on the selectivity towards the desired product.

1. Introduction

Cascade catalysis, where several consecutive reaction steps are performed in one-pot without the separation of intermediate products, has recently attracted considerable attention. The potential benefits in cascade conversions are the decreased production of waste as well as lower equipment costs. The current processes including several separation and reaction steps are time consuming both from the point of development and scaling-up. There exist several examples of cascade catalysis [1], which apply different combinations of catalysts: bio-bio [2], bio-chemo [3] and chemo-chemo [4] cascades. Moreover different reaction steps, like reductions [2], oxidations [5], esterifications [6], decarboxylations [7], etc., have been investigated in cascade conversions. For bio-chemo transformations there are several examples of combining enzymatic and homogeneous catalysis. At the same time one-pot systems, when heterogeneous and enzymatic reactions are efficiently combined are very rare. The main challenge is in rather different experimental conditions required for them, thus the reports in the literature describe systems where heterogeneous and enzymatic catalysis are separated either in space [8] or time [9].

Optically active alcohols are conventionally prepared via kinetic resolution from racemates [10], which implies the intrinsic limitation of 50% yield of the desired enantiomer. In dynamic kinetic resolution (DKR) [11,12], studied especially by Bäckvall and co-workers [12], 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. Additionally zeolites have been reported to be active in the racemization of 1-phenylethanol [8] and Pd/C in the racemization of chiral amines [13]. One potential method to obtain a more environmentally viable process compared to the existing one is to use a cheap raw material, acetophenone, which is hydrogenated to *R*-1-phenylethanol and the formed intermediate is acylated in the same pot to *R*-1-phenylethyl acetate (Fig. 1).

This reaction has been demonstrated over a chemo-biocatalytic system containing both a homogeneous Ru catalyst and an enzyme [14]. Synthesis method could be more industrially attractive, if heterogeneous catalysts could be used instead of a homogeneous counterpart. A sequential method, in which acetophenone was hydrogenated over a heterogeneous Pd/silica/alumina catalyst in the first step followed by the acylation with immobilized enzyme in the second step was recently demonstrated [9]. According to our knowledge, one-pot synthesis of *R*-1-phenylethyl acetate starting from acetophenone hydrogenation, has not been previously performed over a heterogeneous metal-supported catalyst and an immobilized lipase. This approach is successfully demonstrated in the current work over a Pd/MgO catalyst and over an immobilized lipase. Besides the first demonstration of utilization both heterogeneous and enzymatic catalysts in one pot, the main focus of the present study was the effect of the catalyst support.

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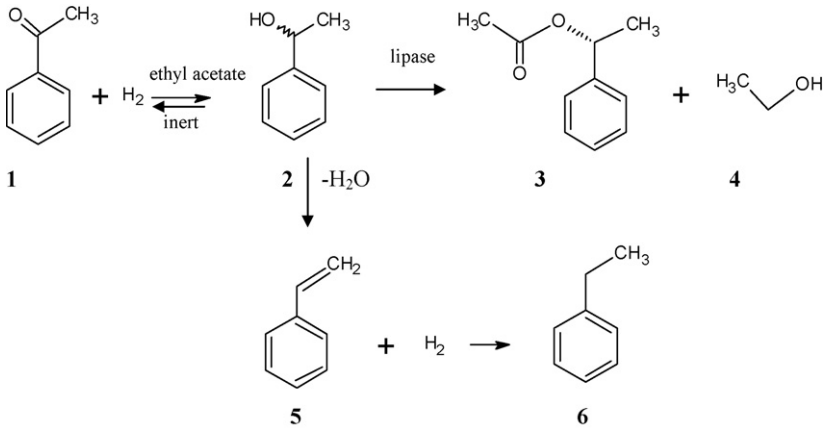

Fig. 1. Reaction scheme for one-pot synthesis of *R*-1-phenylethyl acetate (**3**) from acetophenone (**1**) over chemo-bio catalysts. Other products were *R*- and *S*-1-phenylethanol (**2**), ethanol (**4**), styrene (**5**) and ethylbenzene (**6**) *R*-1-phenylethyl acetate.

2. Experimental

Catalytic hydrogenation of acetophenone (Acros, 99%) was performed in ethyl acetate over four different supported Pd catalysts: 5 wt.% Pd/C (dispersion (*D*%) = 42%, *S* = 1214 m^2/g_{cat}, Aldrich, 5 wt.%), 5 wt.% Pd/Al_2O_3 **I** (Aldrich, *S* = 115 m^2/g_{cat}), 5 wt.% Pd/Al_2O_3 **II** (5 wt.% Pd/Al_2O_3 (UOP) prepared by using aqueous solution of palladium nitrate (Degussa) as precursor and dried at 110 °C and calcined in a muffle oven, *S* = 306 m^2/g_{cat}), 5 wt.% Pd/ZrO_2 prepared from $PdCl_2$ (*D* = 11%, *S* = 75 m^2/g_{cat}) and 5 wt.% Pd/MgO (*D* = 7%, *S* = 106 m^2/g_{cat}). The latter catalyst was prepared in our laboratory by impregnating the predried magnesia (2 g, 20 h, 115 °C) with a solution of Na_2PdCl_4 formed by a reaction between $PdCl_2$ and NaCl at room temperature (stirred 30 min) [7], followed by a treatment with 0.1 mol dm^3 NaOH (1 h). The resulting catalyst was washed with 600 ml of deionized H_2O and dried at 60 °C for 24 h, followed by a reduction and passivation in a tubular oven with controlled gas atmosphere (reduction with heating in flowing H_2 50 ml/min: 2 °C/min to 100 °C; 30 min; 2 °C/min to 250 °C; 2 h; cooling to room temperature and passivation: 1% O_2 in N_2 for 24 h) [17]. Acylation of the formed *R*-1-phenylethanol was performed with Novozym 435 (Lipase B from *Candida antarctica* immobilized on macro-porous polyacrylic resin beads, Sigma). Supported Pd catalysts were prereduced in situ in the glass reactor with flowing hydrogen at 100 °C for 30 min using an electrical heater. Thereafter the deoxygenated reactant, solvent and enzyme catalyst were injected into the reactor under hydrogen flow. After catalyst pre-reduction the reactor was placed in a water bath. Hydrogenation of acetophenone was performed at 1 bar with flowing hydrogen (AGA, 99.999%) at 70 °C, since Novozym 435 was confirmed to be stable at this temperature [12]. Ethyl acetacetate (Fluka, >99%) was used as a solvent, which also acted as an acyl donor for *R*-1-phenylethanol. Typically the hydrogen flow was 295 ml/min. With an overall liquid phase volume of 250 ml, 0.125 g Pd/C and 0.125 g Novozym 435 were used with 0.005 mol of acetophenone. Hydrogenation and acylation were performed in a glass reactor equipped with a motor stirrer made of Teflon. The stirring speed was 380 rpm to ensure efficient mass transfer.

The products were analyzed with a GC equipped with a chiral column (CP Chirasil Dex (250 μm × 250 μm × 25 m)) and with a flame ionization detector. The GC-method was calibrated with the following chemicals: *R*-1-phenylethanol (Sigma), (*R*,*S*)-1-phenylethanol (Fluka, >98%) and ethylbenzene (Fluka, >99%). The products were identified with GC–MS. The water content was analyzed with Karl Fischer titration using Hydranal (Riedel de Häen, Composite 5).

3. Results and discussion

In the preliminary experiments over Pd/C and Novozym catalysts the main reaction product was ethylbenzene with the yield of 62% after 1600 min of reaction time. The choice of palladium for one-pot synthesis was based on the fact, that it has been selective in formation of 1-phenylethanol in acetophenone hydrogenation [15]. Ethylbenzene is mainly formed from the hydrogenation of styrene, which is the dehydration product of 1-phenylethanol, while the yield of the desired product, *R*-1-phenylethyl acetate was below 1 wt.% at the end of the reaction. Ethanol was formed in the stoichiometric amounts related to the desired product (**3** in Fig. 1). This reaction mechanism was confirmed in a separate experiment, in which transformation of 1-phenylethanol was studied under argon atmosphere over Pd/C and Novozym catalysts. As the result from this experiment both acetophenone (88 mol%) and ethylbenzene (10 mol%) were formed as main products at a conversion level of 99% after 2970 min. They are formed via dehydrogenation of 1-phenylethanol leading to hydrogen which can quickly hydrogenate the primary dehydration product of 1-phenylethanol to ethylbenzene. Furthermore, traces of *R*-phenylethyl acetate were observed in the product mixture. The dehydrogenation of alcohols is generally known in literature [16]. Additional route to ethylbenzene could be direct cleavage of C–O bond in the desired product.

In order to suppress the extent of dehydration reaction water with the molar ratio of 0.6 water/reactant was added into the reaction mixture [8]. In this experiment the molar fractions of ethylbenzene and *R*-1-phenylethyl acetate were 45% and 6%, respectively, after 1600 min reaction time. This result was expected, i.e. both the yield of ethylbenzene decreased and the yield of *R*-1-phenylacetate increased when compared with the reaction without water addition (see above). The water addition was not, however, efficient enough to enhance the selectivity to *R*-1-phenylethyl acetate. Actually the enzymatic activity of lipases decreased when using more polar solvents [17,18] indicating that the addition of water is not preferable, when enzyme is present in the reactor.

Since the results with Pd/C catalyst were not very good due to side reactions, three other Pd catalysts were tested in one-pot synthesis of *R*-1-phenylethyl acetate starting from hydrogenation of acetophenone (Table 1).

The highest initial total reaction rates were achieved over Pd/ZrO_2 catalyst followed by Pd/Al_2O_3 **I**, Pd/C, Pd/Al_2O_3 **II** and Pd/MgO. Pd/MgO exhibited the lowest initial rates for all four types of catalysts, which can be explained by the relatively low surface area and low Pd dispersion. Moreover this catalyst was neutralized with NaOH.

Table 1
Catalytic synthesis of *R*-1-phenylethyl acetate (**3**) over several catalysts starting from hydrogenation of acetophenone

Catalyst	Conversion after 1360 min	Molar fraction of **3** (%) after 1360 min[a]	Selectivity to **3** (%)[a]
Pd/MgO	27	8[b] (10)	30[b] (36)
Pd/ZrO_2	98	8	4
Pd/Al_2O_3 (**I**)	97	2	4
Pd/Al_2O_3 (**II**)	46	19 (22)	39 (47)
Pd/C	99	<1	2

Selectivity to **3** is defined as $S = x_3/X$, where x_3 is the molar fraction of **3** and X is conversion of **1**.
[a] Maximum yield or selectivity after 1770 min in parenthesis.
[b] At conversion of 25%.

The conversion levels after prolonged reaction times over the three most active catalysts were close to 100%. Over Pd/MgO the catalytic activity was low and the conversion of acetophenone remained at 28% after 1300 min reaction time.

Over the most active catalyst, Pd/ZrO_2 the initial formation rate for *R*- and *S*-1-phenylethanol was 25-fold the value obtained for Pd/MgO. When plotting the molar fractions of the formed *R*-1-phenylethanol over different catalysts as a function of acetophenone conversion, the slope (defined as the ratio between the changes in the molar fraction of *R*-1-phenylethanol to the changes in the conversion of acetophenone) was 0.5 for all the catalysts being thus independent on the catalyst properties. For Pd/C, Pd/Al_2O_3 **I** and Pd/ZrO_2 catalysts this slope was constant up to 80% conversion. After that, *R*-1-phenylethanol reacted further either to styrene or to *R*-1-phenylethyl acetate. The formed styrene hydrogenated rapidly to ethylbenzene. Dehydration of *R*-1-phenylalcohol was faster over Pd/ZrO_2 than in case of Pd/C and Pd/Al_2O_3 **I** catalysts. Over Pd/Al_2O_3 **II** and Pd/MgO the formation rate of *R*-1-phenylethanol followed an analogous pattern with the other three catalysts up to the conversion level of 28% and 14%, respectively, thereafter the consecutive acylation reaction for *R*-1-phenylethanol became more prominent (Fig. 2).

The second step, enzyme catalyzed reaction of *R*-1-phenylethanol to *R*-1-phenylethyl acetate, was compared over different heterogeneous catalysts combined with an enzyme by calculating the initial acylation rates. They increased with increasing initial hydrogenation and hydrogenolysis rates. Comparison of the ratios between the initial formation rate of *R*-1-phenylethanol and that of *R*-1-phenylethyl acetate ($r_{0,R\text{-}1\text{-}PE}/r_{0,R\text{-}1\text{-}PEaC}$) resulted in the following ranking: Pd/Al_2O_3 **I** (24.1) > Pd/C (14.4) > Pd/Al_2O_3 **II** (12.4) > Pd/ZrO_2 (11.4) ≫ Pd/MgO (1.8). Over a mixture of Pd/Al_2O_3 **II** and Novozym catalysts *R*-1-phenylethyl acetate started to form after 60 min reaction time with a constant rate of 0.002 mmol/(min g_{cat}), which was relatively slow. It was, however, stated in [8] that acylation with ethyl acetate as an acyl donor is a slow reaction compared to e.g. 4-chlorophenyl acetate. On the other hand over Pd/ZrO_2 the initial formation rate of the desired product was very high, 0.037 mmol/(min g_{cat}), but enzymatic activity declined after 400 min which corresponds to a conversion level of acetophenone of about 99%. The formation of *R*-1-phenylethyl acetate is proceeding after prolonged reaction times at a slow rate. The reason for this could be the accumulation of ethanol in the reaction mixture. Enzymatic activity is lower in hydrophilic solvents compared to hydrophobic ones [19]. Ethanol is a stoichiometric by-product from the acylation reaction. According to water analysis with KF-titration the water content was typically around 1 wt.% in the reaction mixture. In a recent publication [10], where the acylation of *R*-1-phenylethyl acetate was carried out over Novozym 435 catalyst with ethyl acetate as an acyl donor, the enzymatic activity was kept high by adding fresh acyl donor, ethyl acetate as well as distilling away ethanol, which by its hydrophilic nature can deactivate the enzyme activity.

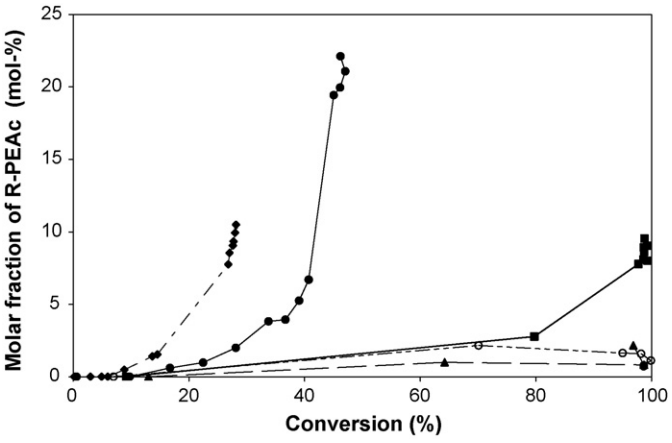

Fig. 2. The molar fraction of **3** as a function of the conversion of **1** over Pd/MgO and Novozym 435 catalysts. Symbols: (◆) Pd/MgO, (○) Pd/C, (■) Pd/ZrO_2 and (▲) Pd/Al_2O_3 **I** and (●) Pd/Al_2O_3 **II**.

The highest molar fractions of the desired products were 22%, 10.5% and 9.6% for Pd/Al_2O_3 **II**, Pd/MgO and Pd/ZrO_2, respectively. The enantiomeric excess of *R*-1-phenylethyl acetate was close to 100% in all the experiments over Novozym 435 catalyst. The maximum theoretical selectivity is 50%. The most selective catalyst was Pd/Al_2O_3 **II** with the selectivity towards **3** being 47% (Table 1). Over Pd/ZrO_2, Pd/Al_2O_3 **I** and Pd/C the maximum molar fractions of the undesired ethylbenzene were 50%, 58% and 66% at close to the 100% conversion of acetophenone. Ethylbenzene started to form to large extent above 95% conversion of acetophenone via fast hydrogenation of styrene, which is an intermediate formed in acid catalyzed dehydration of *R*- and *S*-1-phenylethanol. Acidic supports, even with mild acidity like active carbon and aluminium oxide catalyze dehydration of 1-phenylethylalcohol. The reason for ZrO_2 being active in the dehydration of 1-phenylethanol is the presence of chloride utilized during the catalyst preparation, which makes the catalyst acidic enough to catalyze dehydration reaction.

Over the basic Pd/MgO catalyst and over Pd/Al_2O_3 **II** only traces of ethylbenzene (below 1%) were formed. The latter one is prepared from alumina with very low acidity [20]. Additionally formation of styrene was observed over all catalysts, although the amount of styrene remained below 1%. The low styrene content might be explained by its high hydrogenation rate to ethylbenzene. It was proposed in [21] that in the dehydration of *R*-1-phenylethanol styrene is the first product followed by its hydrogenation to ethylbenzene.

4. Conclusions

It can be concluded that one-pot synthesis of *R*-1-phenylethyl acetate via hydrogenation over heterogeneous catalysts with dihydrogen combined with acylation of the formed *R*-1-phenylethanol over an immobilized enzyme was successfully demonstrated in the current work. The most selective hydrogenation catalyst was a Pd/Al_2O_3 **II** with a low acidity combined with Novozym 435, although it exhibited the second lowest overall activity. If acidic supports are used, the main product is ethylbenzene formed via hydrogenation of styrene, which in turn is a dehydration product of *R*-1-phenylethanol. The future challenge is to achieve high activities and selectivities of the

hydrogenation catalysts in order to get high molar fractions of the optically active esters without deterioration the properties of the enzymatic catalysts.

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