Applied Catalysis A: General 368 (2009) 9–16

Contents lists available at ScienceDirect

Applied Catalysis A: General

journal homepage: www.elsevier.com/locate/apcata

Support influences in the Pd-catalyzed racemization and dynamic kinetic resolution of chiral benzylic amines

Andrei N. Parvulescu, Pierre A. Jacobs, Dirk E. De Vos *

Centre for Surface Chemistry and Catalysis, Department Microbial and Molecular Systems, KULeuven, Kasteelpark Arenberg 23, 3001 Leuven, Belgium

ARTICLE INFO

Article history:
Received 4 June 2009
Received in revised form 24 July 2009
Accepted 28 July 2009
Available online 5 August 2009

Keywords:
Pd catalysts
Basic supports
Chiral amine
Racemization
Dynamic kinetic resolution
Lipases

ABSTRACT

The acid–base properties of the supports for Pd catalysts strongly affect their performance in racemization and dynamic kinetic resolution (DKR) of chiral benzylic amines. The need for a basic support was proven by comparing the racemization results obtained for Pd on silica, on LDH (layered double hydroxide) and on carbon. Pd on amine-functionalized silica proved to be more selective for the racemization of (*S*)-1-phenylethylamine than Pd on alkaline earth supports or Pd on LDH. The difference in selectivity between various Pd catalysts is determined by the rates of formation of the side products. The rate constants of side product formation processes were even higher in the case of Pd/SiO_2 and Pd/C catalysts. The activity of the various catalysts for the rate determining amine dehydrogenation is similar when calculated per surface Pd atom. Combination of a Pd catalyst with *Candida antarctica* lipase B (Novozyme 435) for a one-pot DKR of 1-phenylethylamine gave the best results when Pd on 3-aminopropyl functionalized silica or Pd on 3-(1-piperazino)propyl functionalized silica were used as racemization catalysts, namely 93% yield of the corresponding (*R*)-amide, with 99% e.e.

1. Introduction

Dynamic kinetic resolution (DKR) was recently proposed as a new method for synthesis of enantiomerically pure compounds like chiral amines and alcohols. The process consists of the *in situ* combination of kinetic resolution with a continuous racemization step [1]. DKR starts from racemic mixtures and in principle yields a single enantiomer product with a theoretical 100% yield [1]. While the kinetic resolution is performed by an enzyme, the racemization requires chemocatalysts. The application of this approach to the synthesis of chiral alcohols is already a well established method to produce pure single enantiomers in high yield. Various chemocatalysts such as homogeneous transition metal catalysts, supported metal catalysts or solid acids are used for this purpose [2]. However, reports regarding DKR of chiral amines are quite scarce [3,4]. Most of the racemization catalysts for chiral amines are based on homogeneous complexes of Ru or recently, of dinuclear Ir. As heterogeneous alternatives Pd-containing solids are the most preferred catalysts [3]. Our previous studies regarding the racemization of chiral amines with heterogeneous racemization catalysts indicated that Pd on an alkaline earth support like $BaSO_4$ or $CaCO_3$ is a selective catalyst for racemization of chiral benzylic amines [4]. The nature of the support was found responsible for the limited formation of side products. Based on the kinetics of the reaction a mechanism for racemization of (*S*)-1-phenylethylamine was proposed. According to this mechanism, the side products (Scheme 1) are formed from the reaction of the imine (**2**) with an amine (**1**) resulting in a secondary imine (**3**). The rate constant of this step was small for Pd supported on alkaline earths, while it was high for a support exhibiting even weak acid properties like carbon. In this case the selectivity for the desired amine product was low [4].

Based on these preliminary results we now extend the range of basic supports applied in the racemization of chiral benzylic amines using Pd as active metal. Amine-functionalized silica and layered double hydroxides (LDHs) already found numerous applications as basic catalysts or supports for transition metals in various organic transformations [6]. In this paper we explore the use of these basic supports in the racemization of chiral benzylic amines and compare the activity of the catalysts with that of materials prepared by deposition of Pd on alkaline earth supports and on simple silica. Relations are sought between Pd dispersion, quantified support basicity characteristics and catalyst activity and selectivity. In order to realize the DKR, these catalysts were also combined with an immobilized lipase.

2. Experimental section

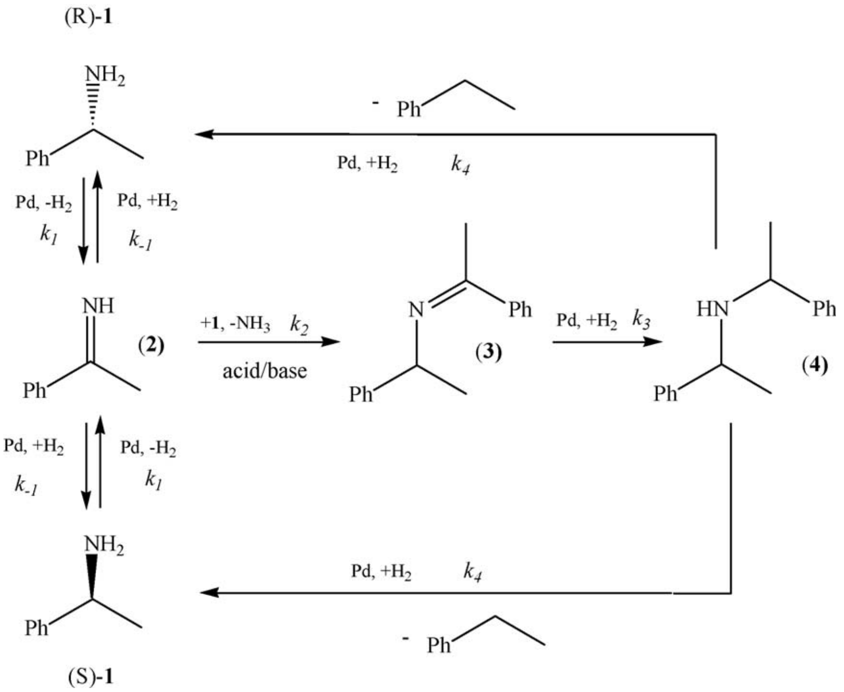
2.1. Materials and catalyst preparation

All reactants were obtained from commercial sources and used as received. Regarding the catalysts, literature procedures were followed for the preparation of Pd/$BaSO_4$, Pd/AP-SiO_2, Pd/PP-SiO_2,

---

* Corresponding author.
E-mail address: dirk.devos@biw.kuleuven.be (D.E. De Vos).

0926-860X/$ – see front matter © 2009 Published by Elsevier B.V.
doi:10.1016/j.apcata.2009.07.042



Scheme 1. Reaction mechanism and rate constants for racemization of (*S*)- and (*R*)-1-phenylethylamine.

Pd/DMP-SiO_2, Pd/LDH and Pd/SiO_2 (A) via the concept of deposition-precipitation [4a]. In these procedures, Pd was reduced with an alkaline solution of formaldehyde using a molar ratio formaldehyde/Pd of 10/1. The catalyst preparation started with dispersing 4 g of support in a solution of the Pd salt in 80 ml of water, and heating for 1 h at 80 °C. A reducing solution was prepared by adding 2 ml of commercial 37 wt.% formaldehyde solution to a 30 wt.% solution of NaOH (2 ml). This reducing solution was then added to the Pd-containing support suspension, and heating was continued for 30 min at 80 °C. At that point, reduction of the Pd was near complete, as evidenced by the black colour of the suspension. The catalyst was isolated by centrifugation, washed abundantly with distilled water and dried under low vacuum at 60 °C overnight. While $PdCl_2$ was used as metal source for Pd/$BaSO_4$ as in Mozingo's method [5], $[Pd(NH_3)_4]Cl_2$ (Aldrich) was used for the other samples since this salt is readily dissolved in water, even without extra HCl. The amount of metal was in each case adjusted to reach a loading of 5 wt.% in the final material.

Pd/SiO_2 (B) was prepared by incipient wetness impregnation using a water solution of $[Pd(NH_3)_4]Cl_2$; the amount of metal was chosen so as to obtain 5 wt.% in the final material. The impregnated material was dried overnight at 100 °C, and then was calcined in O_2 at 450 °C for 150 min and reduced under H_2 at 450 °C for 210 min.

Pd/$CaCO_3$ (5 wt.%) was a gift from Johnson Matthey; Pd/C (5 wt.%) was purchased from Johnson Matthey. AP-SiO_2 is 3-aminopropyl functionalized silica (9 wt.% organic groups), PP-SiO_2 is 3-(1-piperazino)propyl functionalized silica (10 wt.% organic groups) and DMP-SiO_2 is 3-(dimethylamino)propyl functionalized silica (12 wt.% organic groups). All these materials were purchased from Aldrich. As SiO_2, Aerosil 380 from Degussa was used as support. A layered double hydroxide (LDH) was prepared according to reference [7] with general formula $[Mg_4Al_2(OH)_{12}](CO_3)\cdot nH_2O$ and a ratio Mg/Al = 2. *Candida antarctica* lipase B immobilized in acrylic resin (Novozyme 435) was purchased from Aldrich.

2.2. Racemization reactions

10 ml stainless steel autoclaves were used as reaction vessels. The standard racemization conditions were 70 °C, 0.01 MPa H_2, 0.33 mmoles (*S*)-1-phenylethylamine, 4 ml toluene and 40 mg catalyst. For H_2 pressures below 0.1 MPa, a 5% H_2 dilution in N_2 was used as the reactive gas.

2.3. Dynamic kinetic resolution

The one-pot reactions were done in similar conditions as the racemization, using 0.33 mmol racemic 1-phenylethylamine, 4 ml toluene, 100 mg immobilized *Candida antarctica* lipase B (Novozyme 435) as resolution catalyst, 40 mg racemization catalyst and 0.35 mmol acyl donor, 70 °C, 0.01 MPa H_2. At the end of the reaction the autoclave was cooled to room temperature, the catalysts were separated by centrifugation and a sample was taken for further analysis.

2.4. Instrumentation and other methods

XRD measurements were made on a Stoe StudiP diffractometer with Cu $K_{\alpha 1}$ radiation (λ = 1.54 Å). HR-TEM and EDX measurements were performed with a JEOL 4000EX and a Philips CM20 operated at 400 kV. The EDX measurement confirmed for all samples that the Pd catalysts did not contain any traces of Cl ions. Pd particle size was measured in the electron micrographs by averaging over 100 individual particles.

N_2 adsorption-desorption isotherms were recorded on a Tristar 3000 gas adsorption analyzer from Micromeritics. Before analysis the samples were dried under N_2 flow for 10 h at 120 °C. ICP measurements for determining the Pd content of catalysts were made on a Jobin Yvon Ultima instrument.

CO chemisorption measurements were made using an Omnistar TM mass-spectrometer coupled to a Pfeiffer Vacuum pump and an oven with automatic temperature control. The pretreatment procedure was as follows: heating in 10 ml/min H_2 flow with 10° C/min till 70 °C; keeping 1 h under flowing H_2 at 70 °C; cooling down to 25 °C under He flow (10 ml/min) and keeping another 30 min at 25 °C. The measurements were made at room temperature by giving 6.84 μl pulses of CO at regular time intervals.

The basic strength of the supports was evaluated by titration with a solution of benzoic acid (0.01 M) in toluene. The material