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A heterogeneous Ru–hydroxyapatite catalyst for mild racemization of alcohols

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Abstract

Racemization of chirally stable secondary alcohols was performed using a truly heterogeneous catalyst under mild reaction conditions in the absence of any additive or cocatalyst. The catalyst is based on Ru^{3+} immobilized on calcium hydroxyapatite (Ru–HAP). The preparation of the calcium hydroxyapatite (HAP) support and the Ru content and immobilization were optimized leading to maximal catalytic performance. Via combined XRD, Raman, SEM, XPS, EPR, N_2 adsorption, and ICP analysis, information on both the compositional and the structural properties of the material was obtained. The Ru–HAP catalyst is able to racemize benzylic as well as aliphatic secondary alcohols. The catalyst scope was further investigated for racemization of several mono- and polyfunctional secondary alcohols. Performing standard racemization of a reference substrate in the presence of a functional additive demonstrated the inhibitory effect of some of these functions. Finally the heterogeneous nature of the catalyst was verified by filtrate tests.

Keywords: Racemization; Heterogeneous catalysis; Chiral secondary alcohols; Hydroxyapatite; Ruthenium

1. Introduction

Although much effort has been done on asymmetric catalysis during the last two decades, a common and convenient way to obtain enantiomerically pure compounds on industrial scale consists in resolution of racemic mixtures, which are easy to produce and cheap. The theoretical yield of common resolution methods is limited to 50%, which is environmentally or economically not acceptable because of the poor atom economy. Racemization of the unwanted enantiomer can offer a solution to this fundamental problem, since this unwanted enantiomer can be recycled to the resolution step [1,2]. Alternatively, in situ racemization can be applied during the resolution process to obtain a dynamic kinetic resolution (DKR). Clearly, when combined with in situ or ex situ resolution methods, racemization techniques allow surpassing the 50% yield limit, and to reach complete conversion to the enantiopure compound.

Of the existing racemization methods, many focus on chirally labile compounds containing “activated” chiral centers, e.g., cyanohydrins, which can be easily racemized by means of acid, base, or thermal treatment [3]. For the group of chirally stable secondary alcohols or the derived esters, Pd compounds have been shown to be suitable for racemization of secondary allylic esters [4]; Pd and especially Ru complexes have been used as catalysts for the racemization of aliphatic or benzylic secondary alcohols [5–8]. However, several of these alcohol racemization catalysts need additives, such as bases, or the ketones corresponding to the alcohols, and the catalysts are not easily removed from the reaction mixture because of their homogeneous nature.

Until now, only two heterogeneous racemization catalysts have been described for chirally stable substrates: Pd on carbon is a catalyst with moderate activity for 1-phenethylamine racemization under hydrogen atmosphere [9], and acid resins like Amberlyst 15 or Deloxan racemize benzylic alcohols in aqueous media [10,11]. Here we report on heterogeneous catalysts for secondary alcohol racemization, based on Ru ions exchanged on hydroxy-

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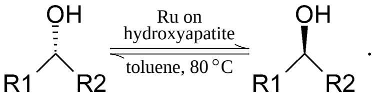
apatite (Ru–HAP):



Ru–HAP has previously been described as an aerobic alcohol oxidation catalyst [12], but when appropriately modified and applied in an oxygen-free atmosphere, it becomes an effective tool for racemization of benzylic and aliphatic secondary alcohols. In the present paper, focus is on optimization of the synthesis procedure as a function of a standard catalytic racemization test, on characterization of the material, and on an exploration of the scope of the catalyst. The hydroxyapatite-based material operates under sufficiently mild conditions to be compatible with resolution techniques and does not need any additive or cocatalyst.

2. Experimental

2.1. Materials

All materials purchased were used as such. Starting materials for catalyst synthesis were $RuCl_3$ hydrate (40–43% Ru, Strem Chemicals), aqueous ammonia solution (ca. 25% NH_3, Riedel–deHaën), $(NH_4)_2HPO_4$ (technical quality, Riedel–deHaën), and $Ca(NO_3)_2 \cdot 4H_2O$ ($> 99\%$, Fluka). Chiral substrates were all $> 99\%$ in *ee* and purity unless otherwise noted: (R)-(+)-*sec*-phenethyl alcohol (Acros), (R)-(−)-2-octanol (Aldrich), (S)-2-hexanol (Aldrich), *trans*-(R, R)-1,2-cyclohexanediol (98%, Janssen), (R)-mandelonitrile (Aldrich), (S)-1-furylethanol (Acros), (S)-(+)-indanol (Aldrich), ethyl (R)-(−)-mandelate (Aldrich), and (R)-(−)-1,2-propanediol (Fluka).

2.2. Support and catalyst preparation

Calcium hydroxyapatite (Ca–HAP) was synthesized following a standardized procedure based on wet precipitation starting from aqueous solutions of $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2HPO_4$ in presence of ammonia [13]. To 47.2 g $Ca(NO_3)_2 \cdot 4H_2O$ (0.2 mol) dissolved in 100 ml deionized distilled H_2O approximately 4 ml of a 25% NH_3 solution in H_2O is added until a pH of 11 ± 0.5 is reached. A second solution is prepared by the addition of 15.85 g $(NH_4)_2HPO_4$ (0.12 mol) to 250 ml deionized distilled H_2O; by adding 25% NH_3 solution in H_2O, the pH of the second solution is increased from 8 to 11. A higher pH value of the starting phosphate solution results in precipitation of the reagent and therefore should be avoided. Under vigorous stirring, the phosphate solution is added to the Ca^{2+} solution using a peristaltic pump at a rate of 4 to 5 ml/h. A white precipitate is formed immediately after the first drops are added. After complete addition the slurry has a pH of about 10 and is stirred for another 2 h at room temperature. Finally, the slurry is aged for 1 h under reflux. After cooling to room temperature, the precipitate is centrifuged (10,000 rpm) and washed twice with 400 ml of deionized distilled H_2O. After freeze drying of the wet cake, the solid yield on phosphate basis amounts to 95%. The XRD diffractogram of the powder confirmed the HAP structure (Fig. 1) and the Ca/P ratio of 1.55 is determined via ICP analysis. *Standard Ru ion-exchange procedure*: 1 g of calcium hydroxyapatite is slurried in 45 ml of deionized distilled water containing dissolved $RuCl_3 \cdot xH_2O$; different ruthenium concentrations resulted in different Ru catalyst loadings. The black suspension is shaken for 24 h at room temperature after which the supernatant is colorless. The solid is washed twice with 45 ml deionized distilled H_2O and centrifuged at 10,000 rpm. Afterward the dark gray cake is freeze-dried resulting in a fine, dark gray powder in quantitative yield.

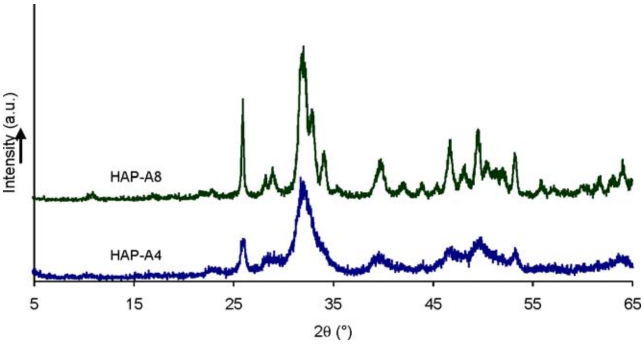


Fig. 1. X-ray powder diffraction patterns of HAP supports. Both samples were prepared starting from $Ca/P = 1$, but were aged for 1 h at 40 °C (HAP-A4) or for 2 h at 100 °C (HAP-A8).

2.3. Standard racemization reaction

Standard reactions were performed at a reaction temperature of 80 °C in well-stirred glass batch reactors (8 ml, 900 rpm) containing 5 ml of toluene and 0.26 mmol chiral alcohol substrate S (*ee* $> 99\%$). Depending on its Ru content, the amount of Ru–HAP was chosen so as to get a S/Ru ratio of 33. In the case of 2 wt% Ru–HAP, this corresponds to 40 mg of catalyst for a 0.26 mmol reaction. After all components were introduced into the reactor, the reaction mixture was flushed with an inert gas to minimize substrate oxidation owing to residual oxygen, and the reactor was closed with a crimp cap. Degassing with 3 vacuum-N_2 cycles using a Schlenk line did not result in lower amounts of oxidation products. Samples were withdrawn through the rubber septum and analyzed on a HP 6890 GC equipped with a CP-CHIRASIL-DEX CB column (0.32 mm × 0.25 µm × 25 m) and FID detection.

2.4. Instrumentation

XRD measurements were performed with a Siemens D5000 diffractometer with filtered Cu-K_α radiation (40 kV and 50 mA). Raman spectra were recorded with a Bruker Equinox 55 with 1064 nm Nd:YAG excitation. The ICP measurements were carried out using an ICP-OES apparatus Perkin-Elmer Optima 3300 DV. Elemental analysis (Ca, P, and Ru) of the support and catalyst was performed by ICP after the solids were completely dissolved using diluted HNO_3. N_2 adsorption measurements were carried out with a Coulter Omnisorp 100 apparatus. Electron micrographs were obtained with a JEOL JXA 733 apparatus. XPS measurements were performed with a Perkin-Elmer PHI 5500 ESCA system, with monochromated Al-K_α radiation (1486.6 eV). Peak deconvolution was performed assuming a Gaussian–Lorentzian peak shape, resulting in a goodness of fit smaller than 1. For EPR measurements, a Bruker ESP 300 spectrometer with cooling accessory down to 120 K was used at X-band ($\sim$ 9.59 GHz).

3. Results and discussion

3.1. Catalyst characterization

The calcium hydroxyapatite structure of the catalyst support material was confirmed by XRD measurements before and after ion exchange (Fig. 1); the patterns are in good agreement with reported data [14]. The absence of RuO_2 in the exchanged samples, even at high Ru loadings, was verified before and after reaction using XRD. The structural identity of the parent HAP material was also confirmed by Raman vibrational spectroscopy (Fig. 2). The HAP displays PO_4 vibrational frequencies that are well distinguishable from those of potentially contaminating, phosphate-containing phases. In agreement with the literature [15], bands were observed at 964 cm^{-1}, for the symmetric P–O stretching ν_1, at 1053 and 1077 cm^{-1} for the asymmetric P–O stretching ν_3, and at 432, 451, 582, 592, and 611 cm^{-1}, for the O–P–O bending modes ν_2 and ν_4. Unfortunately, no Raman spectra could be recorded for the dark-colored Ru-containing samples.

A 2 wt% Ru–HAP catalyst sample, synthesized under standard conditions (vide supra), was further thoroughly characterized by several other techniques. N_2 adsorption was performed at 77 K after pretreatment of the 500-mg samples at 200 °C under high vacuum for 12 h. The specific surface area was calculated by means of the Brunauer–Emmett–Teller (BET) equation. The surface area for the standard HAP and RuHAP was 99 and 115 m^2/g, respectively, and is therefore only marginally influenced by the ion exchange with Ru. As expected, hardly any microporosity was detected as can be seen in the adsorption–desorption isotherms (Fig. 3). The specific areas obtained with this wet synthesis are substantially higher compared to other synthesis methods [16]. The morphology of the apatite crystals was investigated by SEM and shows irregular crystalline shapes and a rough crystal surface. Crystal sizes ranging from 2 to 20 µm were observed. No obvious morphological difference could be seen between HAP (Figs. 4a and b) and Ru–HAP (Fig. 4c).

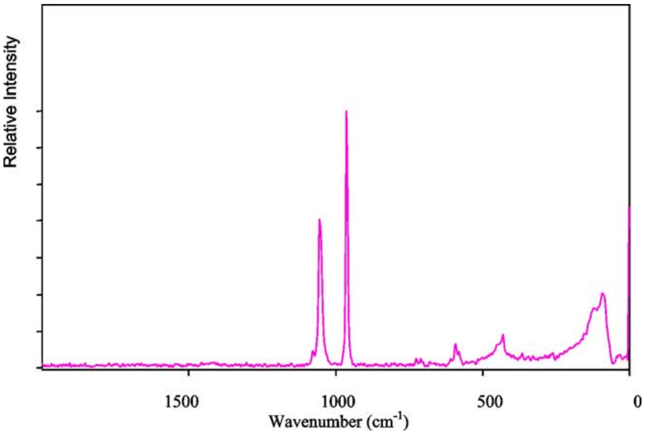


Fig. 2. Raman spectrum of a standard HAP support.

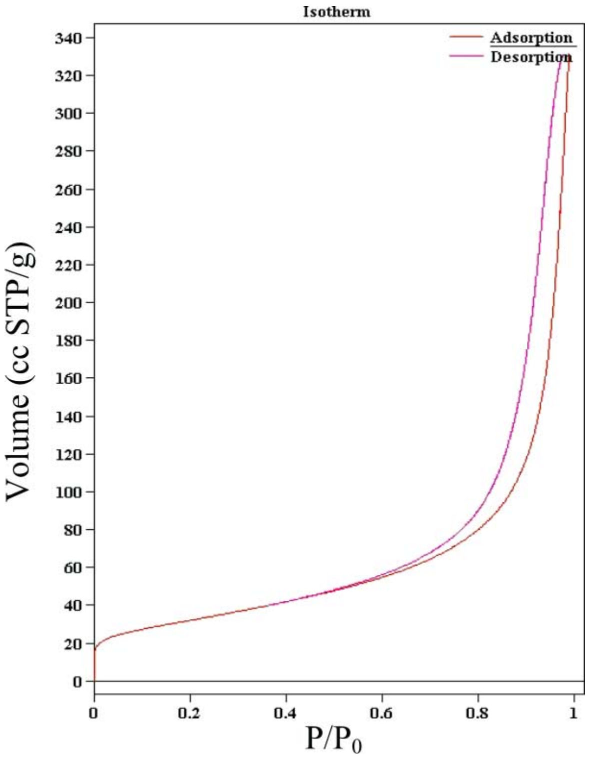


Fig. 3. N_2 adsorption–desorption isotherms (77 K) of a standard RuHAP catalyst.

The surface compositions (Ca, P, O, and Ru) of the standard support material and of the Ru catalysts were investigated using XPS. Ca/P ratios were calculated and compared with the ICP analysis data of the bulk materials. As can be seen in Table 1, the standard support is slightly Ca deficient compared to a stoichiometric Ca–HAP ($Ca_{10}(PO_4)_6(OH)_2$) in which the Ca/P ratio is 1.67. The composition of Ca^{2+}-deficient HAP can be described by $Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$. When Ru^{3+} ions are exchanged on the HAP surface, the Ca/P ratio of the bulk material decreases because the Ca^{2+} ion with its twofold positive charge is partially replaced by Ru^{3+}, likely in association with an anion such as Cl^- or OH^-. This trend is also

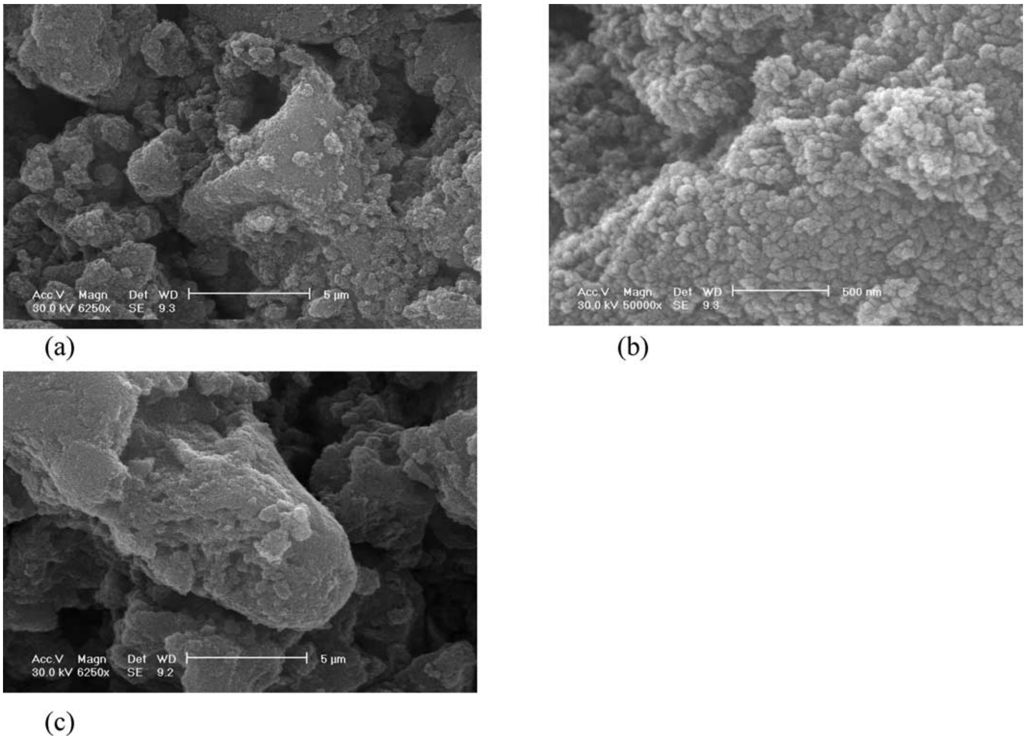


Fig. 4. SEM micrograph images of a standard HAP (a, b) and 2 wt% standard Ru–HAP (c).

Table 1
Determination of the surface and bulk composition of the standard catalyst support and standard 2 wt% catalyst

Sample	(Ca/P) ICP	(Ca_{2p}/P_{2p}) XPS	Wt% Ru ICP	Ru/ (Ru + Ca) ICP	Ru/ (Ru + Ca) XPS
HAP	1.55	1.31	0	0	0
0.5 wt% Ru–HAP	1.53	1.36	0.4	0.0042	0.05
2 wt% Ru–HAP	1.50	1.25	1.31	0.0137	0.128

clear in the XPS measurements, and for the 2 wt% Ru–HAP samples, a Ca/P XPS ratio as low as 1.25 was recorded. The Ru/(Ru + Ca) elemental ratios obtained via XPS are about 10 times higher than those measured for the bulk samples via ICP. This indicates that the Ru does not deeply enter into the nonporous HAP crystallites, which may well be desirable if access of the organic molecules to the Ru centres is required. No chlorine XPS line could be detected on the surface of the 0.5 wt% Ru–HAP or 2 wt% Ru–HAP samples. This contrasts with the findings of Kaneda and co-workers who suggested, based on XANES data, that a Ru^{3+}(Cl) monomer was present on the surface of the Ru-exchanged HAP [12]. However, the sample studied in this XANES study contained 17 wt% of Ru; the much lower Ru content of our samples (0.5–2 wt%) might be one of the factors at the origin of the observed difference.

The oxidation state of the Ru ions was also investigated by XPS analysis. The binding energy (BE) of the Ru $3d_{5/2}$ signal is evaluated since reference data are mainly available for this electron level. The BE of the carbon 1s was taken as the reference at 284.9 eV. The Ru $3d_{3/2}$ signal is completely convoluted with the C1s signal of some carbon impurity, but a BE of 281.3 eV can be well discerned for the Ru $3d_{5/2}$ level. Metallic Ru^0 invariably has binding energies at 279.8 ± 0.2 eV; for RuO_2, 281 eV and 282.1 eV have been found; $RuCl_3$ has 281.8 eV [17]. The value of 281.3 eV observed for Ru–HAP therefore is clear evidence that the Ru on the hydroxyapatite is in an oxidized state, probably Ru^{3+} or Ru^{4+}.

EPR spectra were recorded with an X-band spectrometer at 120 K. Hydrated Ru–HAP samples with 0.5, 1, and 2 wt% Ru display similar spectra, even if the spectra are less well resolved for the samples with higher Ru concentration. In the 0.5 wt% sample, a single species prevails; its spectrum can be satisfactorily fitted with the Q-Pow software [18], assuming as parameters $g_1 = 2.31$, $g_2 = 2.06$, $g_3 = 1.93$ (Fig. 5). These parameters are characteristic for a rhombic Ru^{3+} species. Similar rhombic spectra have for instance been recorded for Ru^{3+} coordinated by the lattice oxygen atoms of a zeolite Beta [19].

Summarizing, the data give evidence for the presence of mononuclear, Cl-free Ru^{3+} centres, mainly located at the outer rim of the HAP crystals.

3.2. *Racemization of 1-phenethyl alcohol with Ru–HAPs derived from various HAP precursors*

In order to evaluate the utility of Ru-containing HAPs as catalysts for the racemization of chiral alcohols, test reactions were conducted in which the enantiomer distribution

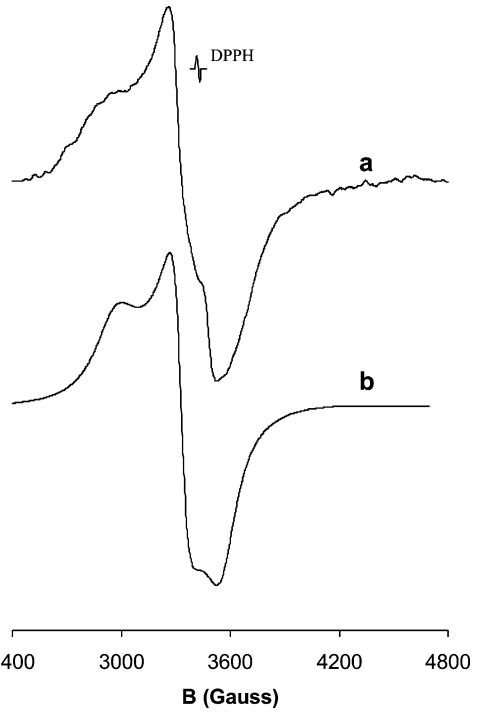


Fig. 5. EPR spectrum of (a) a 0.5 wt% Ru–HAP at 120 K and (b) a simulated spectrum assuming as parameters $g_1 = 2.31$, $g_2 = 2.06$, $g_3 = 1.93$.

Table 2
Synthesis parameters for different HAP supports

Sample	Molar ratio reagents	Aging time	Aging temperature (°C)	Ca/P ICP
HAP-A1	1	1 h	20 °C	1.31
HAP-A2	1	5 h	20 °C	1.23
HAP-A3	1	20 h	20 °C	1.39
HAP-A4	1	1 h	40 °C	1.38
HAP-A5	1	5 h	40 °C	1.40
HAP-A6	1	< 1 h	100 °C	1.43
HAP-A7	1	1 h	100 °C	1.45
HAP-A8	1	2 h	100 °C	1.45
HAP-A9	1	20 h	100 °C	1.50
HAP-B1	1.67	1 h	100 °C	1.55
Standard	1.67	1 h	100 °C	1.55
HAP-B2	1.67	4 h	100 °C	1.60
HAP-B3	1.67	24 h	100 °C	1.60
HAP-B4	1.67	5 d	100 °C	1.61
HAP-B5	1.67	9 d	100 °C	1.64
HAP-B6	1.67	16 d	100 °C	1.59

of 1-phenylethanol was followed as a function of time starting from pure (*R*)-1-phenylethanol. The synthesis of HAPs under different conditions leads to widely dissimilar materials. Particularly the Ca/P ratio of the Ca–HAP material ($Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$) is sensitive to different synthesis parameters, such as the molar Ca/P ratio of the reagents, the aging time, and temperature. Two series of supports were prepared starting from Ca/P molar ratios of 1 and 1.65 (HAP-A1 till HAP-A9 and HAP-B1 till HAP-B6, respectively) (Table 2). Aging temperatures were varied from 20 to 100 °C and aging times ranged from 1 h up to several days. The data of Table 2 clearly show that increasing aging temperature and aging time generally result in higher Ca/P ratios; at the same time, more crystalline materials with larger particle dimensions are obtained, as can be judged from the peak width at half height of X-ray diffraction signals (Fig. 1).

All these HAP samples were transformed into 2 wt% catalyst samples by standard ion exchange. A blank reaction with a Ru-free material was performed as well; no inverted product could be detected. Fig. 6a shows an obvious correlation between the Ca/P ratio of the Ru-containing material and the activity in the racemization reaction of (*R*)-1-phenylethanol: higher Ca/P ratios of the support resulted in higher activity of the corresponding catalyst. A similar trend is derived from Fig. 6b, where the concentration of inverted alcohol is plotted versus the peak width at half height of the 002 reflection at $2\theta = 25.8°$. Clearly, the activity of the Ru increases as the X-ray diffractogram of the support material shows less broadened diffraction signals. Based on these experiments, a standard procedure for HAP preparation was defined, consisting of room temperature precipitation with a 1.67 Ca/P ratio in the reagents, followed by aging for 1 h

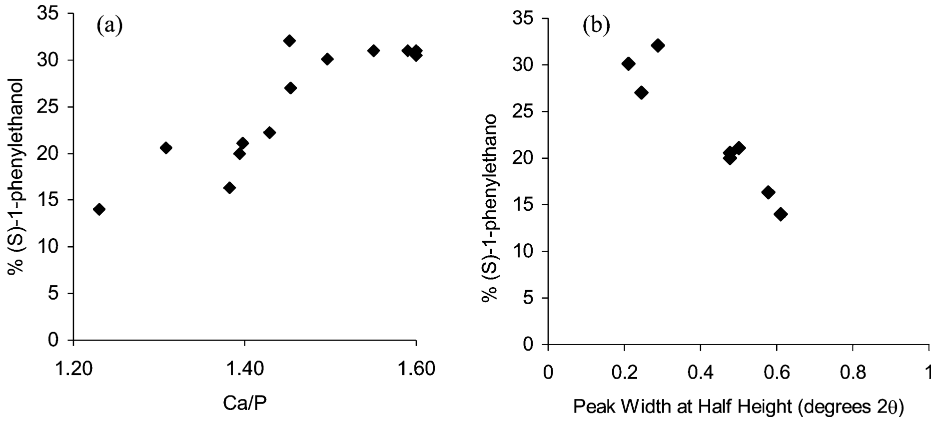


Fig. 6. (a) Racemization activity of 2 wt% Ru sample vs Ca/P ratio of HAP supports as determined by ICP. The racemization activity is expressed as yield of (*S*)-1-phenylethanol after 4.5 h standard racemization of (*R*)-1-phenylethanol. (b) Racemization activity vs crystallinity of HAP support (expressed as width at half height of the 002 diffraction signal at $2\theta = 25.8°$). Racemization activity as in (a).

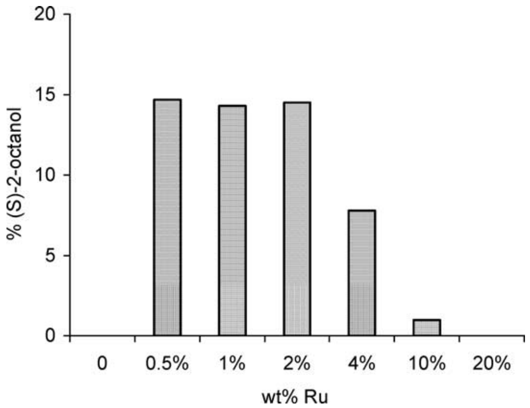


Fig. 7. Influence of the Ru loading of the standard support HAP. Yield of (S)-2-octanol given after 1 h standard racemization reaction (S/Ru = 33) of (R)-2-octanol.

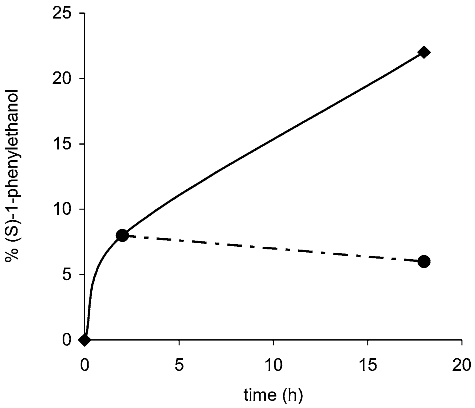


Fig. 8. Heterogeneity test for standard racemization reaction of (R)-1-phenylethanol. The evolution of the reaction in the suspension (full line) and in the clear filtrate (dotted line) is shown.

at reflux. For this HAP, the Ca/P ratio amounted to 1.55 according to ICP analysis.

3.3. *Influence of Ru concentration, precursor, and solvent*

In previous work on Ru–HAP catalysts, a 17 wt% Ru–HAP material was employed for the aerobic alcohol oxidation [12]. In the case of alcohol racemization, the relationship between catalyst activity and Ru content is clearly different, as is evident from Fig. 7. Starting from a standard HAP support, 6 different Ru loadings between 0.5 and 20 wt% were prepared. After 1 h in the racemization of (R)-2-octanol, the percentages of inverted alcohol were compared (Fig. 7). The mass of the catalysts was adjusted, so that each reaction contained the same molar amount of Ru (S/Ru = 33). Clearly, there is a major activity decrease when Ru loadings exceed 2 wt%. At high loadings of 10 wt% or more, no racemization activity could be measured at all, in contrast with the data reported for alcohol oxidation.

Besides $RuCl_3 \times xH_2O$, other Ru sources such as $RuBr_3 \times xH_2O$ and $Ru(OAc)_3$ may be used in the ion exchange. Ion exchange of $RuBr_3 \times xH_2O$ was performed in an identical way as ion exchange of $RuCl_3 \times xH_2O$. On the contrary, ion exchange of $Ru(OAc)_3$ on HAP was unsuccessful at room temperature; in order to obtain complete uptake of Ru^{3+} by the HAP, ion exchange at 70 °C for 24 h was necessary, as indicated by a colorless supernatant. Three catalysts, viz. Ru–HAP–Cl, Ru–HAP–Br, and Ru–HAP–OAc containing 2 wt% of Ru were prepared starting from a freshly prepared HAP (Ca/P ratio 1.31), and their respective activity was evaluated in the racemization of (S)-1-indanol. While the eventual result after 30 h is similar, the catalysts prepared from Ru acetate and particularly Ru bromide display a higher initial activity.

A limited solvent screening showed that many apolar solvents are suitable for the reaction. In the racemization of (S)-1-indanol using a 2 wt% RuHAP (Ca/P = 1.3), the following order was obtained after 20 h of reaction: m-xylene (39% of (R)-1-indanol) > PhCl (35%) > n-heptane (31%) > toluene (23%) > THF (17%). However, solvents with strongly coordinating groups should be avoided; thus no activity was observed in tertiary butanol.

3.4. *Heterogeneous nature of the catalyst and comparison with a homogeneous catalyst*

In order to prove the heterogeneous nature of the catalyst and the absence of Ru leaching, a filtration test was performed, in which the catalyst was separated from the reaction suspension at approximately 10 % conversion of the starting enantiomer through filtration (0.2 µm) at reaction temperature. The reaction progress in the filtrate and in the suspension is further monitored (Fig. 8). No further racemization occurs even at extended times, indicating that no active species leach from the support during reaction. Concerning the reuse of the RuHAP catalyst, it was observed that upon second use, the catalyst conserved less than 50% of its original activity. At present, several methods are being investigated to restore the original activity, e.g., by desorption or calcination of residual adsorbed products.

The activity of the optimized RuHAP system was compared to that of $[Ru(p\text{-cymene})Cl_2]_2$ and of the Shvo-complex, two reported homogeneous ruthenium complexes with racemization activity. In addition, a comparison was made with four commercially available heterogeneous metal catalysts. All reactions were performed under identical conditions (80 °C in toluene and S/metal ratio of 33). In the case of the dimeric ruthenium Shvo-complex, a S/Ru ratio of 16.5 was also tested because in this case, only one of both Ru atoms is involved as a catalytic species [6]. The $[Ru(p\text{-cymene})Cl_2]_2$ was tested in presence and absence of an excess of Et_3N as base. The results shown in Fig. 9 reveal that RuHAP is a competitive and attractive racemization catalyst compared to homogeneous systems which are not easily separated from the product, while RuHAP can be easily removed by filtration when the reaction is complete.

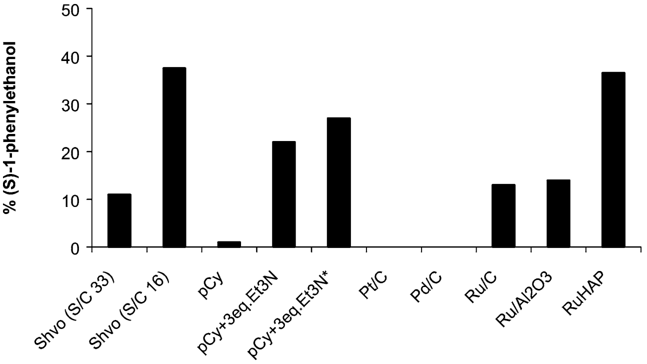
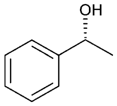
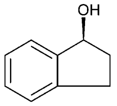
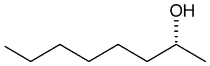
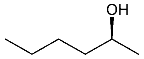
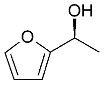
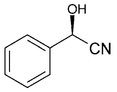
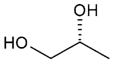
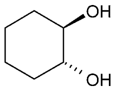
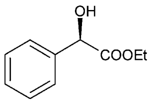


Fig. 9. Comparison under identical conditions ($S/C = 33$, toluene, 353 K) of the heterogeneous RuHAP catalyst with homogeneous Ru complexes and commercial 5 wt% heterogeneous transition metals in the racemization of (R)-1-phenylethanol (pCy = $[Ru(p\text{-cymene})Cl_2]_2$). Percentage inverted alcohol was measured after 6 h ($*$ reaction performed at room temperature in dichloromethane).

Table 3
Racemization of different chiral alcohol substrates[a]

Entry	Substrate	Time (h)	*ee*	Yield (%)
1		20	13	92
2		20	34	91
3		20	6	94
4		20	6	93
5		24 48 96	60 29 6	83 75 65
6		24	43	98
7		48	100	100
8		48	100	100
9		24	100	100

[a] Conditions: 0.26 mmol of chiral alcohol, 40 mg of 2 wt% standard RuHAP ($S/Ru = 33$), 5 ml toluene, inert atmosphere, 353 K.

3.5. *Scope of the catalyst*

The standard 2 wt% Ru–HAP catalyst was used for the racemization of several enantiomerically pure secondary alcohols at 80 °C and a S/Ru ratio of 33. In Table 3, the *ee*'s and yields measured after given times are recorded. The broad scope of the Ru–HAP system is demonstrated by its ability to racemize α-aryl as well as aliphatic secondary alcohols within relatively short reaction times. This is exemplified by the reactions of representative 1-arylalkanols (entries 1 and 2), 2-alkanols (entries 3 and 4), 2-furylethanol (entry 5), and mandelonitrile (entry 6). The selectivity for oxidized side-products is in all cases below 10%; for 1-furylethanol some degradation occurs at long reaction times. Reaction of the allylic alcohol 1-octene-3-ol in presence of Ru–HAP resulted in fast and quantitative isomerization to the saturated 3-octanone. This behavior is quite frequent for the combination of an allylic alcohol with Ru or another transition metal catalyst [20]. It should be noted that for epimerization of allylic esters, a practical solution is already available via Pd catalysis [4].

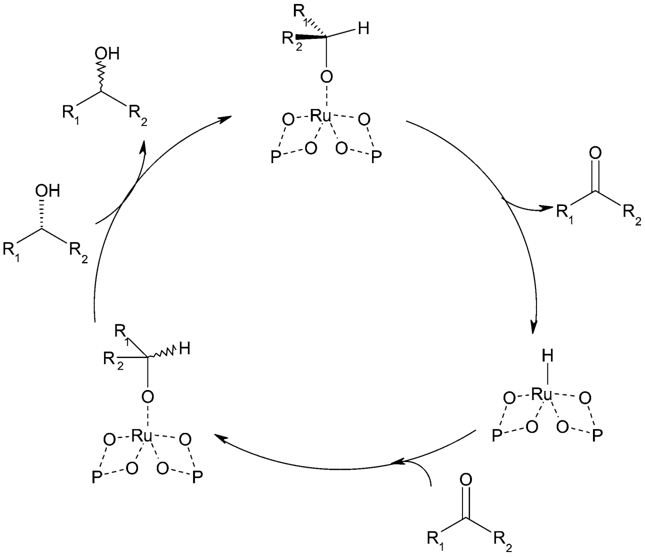
A more substantial limitation of the Ru–HAP catalyst is that it is hardly active with strongly coordinating species like vicinal diols (entries 7 and 8) as well as α–hydroxyesters (entry 9). In these cases, no oxidation products were observed either.

3.6. *Influence of specific organic functions on the activity and mechanism*

In order to study the functional group compatibility of the Ru–HAP catalyst, a 20 h standard racemization of (R)-1-phenylethanol was performed in presence of 10 mol% of a functional additive, relative to the substrate. This approach was used because of the limited choice of commercially available and cheap polyfunctional chiral alcohols. Comparison of the *ee* values in reactions with or without the additive then allows evaluation of whether certain functions have an inhibitory effect on the catalytic racemization activity.

Primary, secondary, and aromatic amines inhibit the reaction completely, just like carboxylic acids and, to a lesser extent, esters. In the case of the esters, it cannot be excluded that a small amount of the ester is hydrolyzed to the free acid; adsorption of the latter as a carboxylate on the active site might well explain the inhibitory effect. Efforts to prevent ester hydrolysis through catalyst predrying remained unsuccessful. In contrast, tertiary amines, ketones, and alcohols such as phenols do not seriously affect the racemization rate. Addition of 10 mol% of the ketone acetophenone had no influence on the reaction rate of 1-phenylethanol nor on the amount of oxidized substrate. Unfortunately, these findings imply that the Ru–HAP racemization catalyst cannot be used in the same pot with lipases that kinetically resolve alcohols through transesterification. Indeed, in such kinetic resolutions, esters are the products, and these are expected to inhibit the Ru–HAP catalyst, even if we have observed that the Ru–HAP catalyst itself does not affect the activity of the enzyme (Novozym435). In all cases where a homogeneous Ru racemization catalyst has been employed in combination with a lipase, a substantial activity decrease or even a total deactivation of the Ru catalyst has been observed [7].

The effect of different diols on the racemization activity of Ru–HAP shows that irreversible coordination might well



Scheme 1.

be the source of the catalyst inhibition. Thus, at a diol concentration of 10% with respect to the substrate, the chelating diols 1,2-propanediol and 2,4-pentanediol totally inhibit the catalyst, while activity is partially preserved in the presence of the less strongly chelating 2,5-hexanediol.

As a possible cycle for this catalytic racemization, a pathway starting with the formation of a Ru–alcoholate species and subsequent β-hydride elimination to form the corresponding ketone seems plausible (Scheme 1). The HAP support, which has an alkaline surface pH, may well assist in the deprotonation of the alcohol, and thus replace the dissolved base, e.g., an alkylamine, which is used as a necessary additive for some homogeneous Ru catalysts. After elimination of the ketone, a Ru–hydride species is formed which is able to reduce the formed ketone back to either enantiomer of the alcohol. The proposed mechanism is consistent with the observation that alcoholic solvents, such as tBuOH, inhibit the catalysis by coordinating on the Ru. Whether the intermediate ketone stays coordinated to the catalytic Ru^{3+} center or leaves and recoordinates during the reaction cycle is not clear; one may even envisage that both alcohol and ketone coordinate to the Ru^{3+}, resulting in direct hydride transfer from alcohol to ketone. In the latter case, the cycle is virtually identical to that of Meerwein–Ponndorf–Verley reductions.

4. Concluding remarks

In summary, immobilized ruthenium on hydroxyapatite was found to be an efficient heterogeneous catalyst for secondary alcohol racemizations. Because of the proven heterogeneity, the catalyst can be recovered by simple filtration. This racemization approach can be sequentially combined with classical kinetic resolution or chiral chromatography, e.g., via chiral simulated moving-bed chromatography, resulting in enhanced yields of enantiomerically pure products starting from racemic mixtures. Several α-benzylic and aliphatic alcohols could be racemized under mild reaction conditions (80 °C in toluene) in a substrate to catalyst ratio of 33. The procedure takes place within reasonable reaction times and in absence of any additive or cocatalyst.

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