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A zeolite–enzyme combination for biphasic dynamic kinetic resolution of benzylic alcohols

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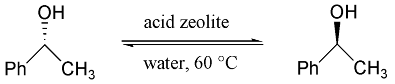
Acid zeolites like H-Beta are efficient heterogeneous catalysts for racemization of benzylic alcohols in water; by combination of the racemization with an enzymatic kinetic resolution in a two-phase system, enantiomerically pure esters were obtained in high yield *via* a dynamic kinetic resolution.

Resolution of cheap racemic mixtures, *e.g.* using enzymes, is a common route to the production of enantiomerically pure chemicals on an industrial scale. However, the chemical yield of a classical resolution is limited to 50%, and this has spurred efforts to combine kinetic resolution with *in situ* racemization of the undesired enantiomer. The resulting *dynamic kinetic resolution* (DKR) gives a high and enantiopure yield starting from a racemic mixture. Equilibration of the enantiomers is easy for chirally 'labile' compounds such as cyanohydrins, using acid, base or thermal treatment;[1] but racemization requires a specific catalyst for many other compounds, including secondary alcohols or amines. Transition metal catalysts for racemization were successfully combined with enzymes in the DKR, as shown in a recent review by Bäckvall *et al.*,[2] and have been applied on an industrial scale.[3] Besides homogeneous Ru, Pd, *etc.*, only two heterogeneous catalysts based on transition metals have been described in this respect: Pd/C has a moderate catalytic activity for 1-phenethylamine racemization under H_2,[4] and Ru immobilized on hydroxyapatite[5] racemizes benzylic and aliphatic alcohols. Reports on the use of heterogeneous acids are limited to acid polymers like Amberlyst®15 and Deloxan™ which have been used for benzylic alcohol racemization in aqueous media.[6]

We here report the first application of acid zeolites as heterogeneous catalysts for benzylic alcohol racemization, and the use of these efficient racemization systems in a new aqueous biphasic dynamic kinetic resolution.

While zeolites are well known as solid acids in *e.g.* hydrocarbon reactions, some zeolites can even be applied in aqueous conditions due to their stability and hydrophobicity.[7] In the case of alcohol racemization in aqueous media, zeolites appear to be a new, efficient and cheap racemization tool (Scheme 1).



Scheme 1

The investigation started with a screening of different acid zeolites for their activity in the racemization of (*R*)-1-phenylethanol. Reactions were performed in a glass batch reactor at 60 °C under air using 0.26 mmol (*R*)-1-phenylethanol substrate in 5 ml distilled water in the presence of 80 mg of zeolite. The reaction slurry was stirred vigorously and the ee of the substrate was monitored.† Substrate concentrations below 50 mM were employed to circumvent any condensation of the carbocation intermediate and alcohol substrate resulting in an ether dimer side product.‡ The use of water as a solvent also impedes the formation of by-products like (poly)styrene. Selected results after 2 h reaction with different zeolites are presented in Table 1 (entries 1–6), and are compared to the performance of other acid catalysts (entries 7–10).

In the case of faujasite (H-USY) or mordenite type zeolites, racemization activity was only obtained for sufficiently dealuminated materials, with Si/Al ratios of 10 or more. This indicates that the racemization requires a sufficient acid strength. However, from the selected screening results, H-Beta zeolites (3 different batches from PQ) are clearly superior to the other zeolite types. Complete racemization could be achieved within 2 h at 60 °C with a commercial H-Beta zeolite (CP814E-22). Substantial activity was also obtained with an H-MCM-22 zeolite, which shares many characteristics with H-Beta, such as small crystal size, high Si/Al ratio, and affinity for hydrophobic compounds. Other zeolites, as well as the acid resins described in the patent literature, require substantially longer reaction times to reach complete racemization. Remarkably, the H-Beta zeolite is even much more active than 0.5 M of a dissolved strong acid such as *p*-toluenesulfonic acid (entry 10). A clear advantage is that in the presence of the strong acid zeolite, the aqueous reaction medium is essentially neutral ($pH_{water} = 7$). This makes, together with the stability and possible re-use of the H-Beta zeolite, the material a suitable candidate for application in a dynamic kinetic resolution.

The main problem in combining the acid-catalyzed racemization with enzymatic resolution by esterification is that the reactions occur under aqueous and water-free conditions respectively. This necessitates the physical separation of the two reactions in two different phases, *viz.* a water layer for zeolite-catalyzed racemization and a water immiscible solvent containing the lipase for the resolution reaction. These reaction requirements are fulfilled in the reaction setup depicted in Fig. 1. The biphasic reaction concept is frequently used in biotransformation technology,[8] but this is the first report of a simultaneous combination of bio- and chemocatalysis in two different phases. The reactor is equipped with a rotating basket with an inox gauze, suspended in the organic phase and containing immobilized *Candida antarctica* lipase B (Novozym 435®). In this way the enzyme is excluded from the aqueous zeolite suspension; consequently, the enzyme-catalyzed hydrolysis of the product ester and of the acyl donor is minimized. The stirring rate was adjusted to 300 rpm to realize efficient

Table 1 Racemization of (*R*)-1-phenylethanol in water at 60 °C[a]

Entry	Catalyst	Si/Al	*t*/h	ee (%)
1	H-USY	15	2	73
2	H-MCM-22	15	2	40
3	H-Mordenite	10	2	31
4	H-Beta CP814E 22	11	2	0
5	H-Beta CP806B 25	12.5	2	4
6	H-Beta CP811BL 25	12.5	2	6
7	Amberlyst® 15	—	2	46
8	Nafion® on SiO_2[b]	—	2	55
9	Dowex® 50X8-100	—	2	67
10	0.5 M PTSA	—	2	12

[a] Reaction conditions: 0.26 mmol (*R*)-1-phenylethanol (99% ee), 5 ml water, 60 °C, 80 mg zeolite or resin. [b] Nafion® SAC13.

mass transfer of the substrate between the layers at any time during the reaction, while avoiding turbulent phase mixing.

Biphasic dynamic kinetic resolutions were performed with 1.27 mmol racemic 1-phenylethanol, 50 ml water and 50 ml organic solvent, 11 or 110 mg Novozym 435®, 413 mg H-Beta zeolite and the acyl donor. Enzyme and zeolite amounts were chosen in order to match the rates of resolution and racemization, and to avoid depletion of the transformed alcohol enantiomer, which is a basic requirement for DKR.[9] A key concern is to minimize side reactions in the water layer *viz.* acid-catalyzed (trans-)esterification leading to lower product ee's, and hydrolysis of the acyl donor. Both reactions are avoided by increasing the log*P* of the acyl donor, and thus excluding it from the water. Instead of the common acyl donors vinyl acetate and isopropenyl acetate (Table 2, entries 1 and 2), the more apolar vinyl octanoate and vinyl laurate were employed (entries 3 and 4). A yield increase is observed using 2 equivalents of vinyl octanoate; with vinyl laurate, the rate of the enzymatic resolution decreases considerably. In a second complementary strategy, the water activity in the organic layer, which causes enzyme-catalyzed hydrolysis of acyl donor and product, was minimized. When instead of toluene, octane is used, an obvious yield increase is perceived, but in tetradecane, the enzyme activity decreases dramatically (entries 5, 3 and 6). Hence the combination of octane as solvent and vinyl octanoate as acyl donor seems most optimal (entry 7). By gradually adding the acyl donor to the octane–water biphasic DKR system, at a rate of two equivalents of vinyl octanoate per h, high yields of enantiopure ester can be obtained. After 1.5 h, the 50% border is crossed and at 8 h, or 16 eq. of acyl donor, the yield amounts to 90%, with an ee exceeding 99% (entry 8). High yields of the enantiopure ester can also be obtained for other benzylic alcohols such as 1-(*p*-tolyl)ethanol; the efficient racemization of aromatic substrates with electron-donating groups is in agreement with the carbenium ion intermediate of the racemization. As expected, racemization of 1-(*p*-BrC_6H_4)ethanol was slower.

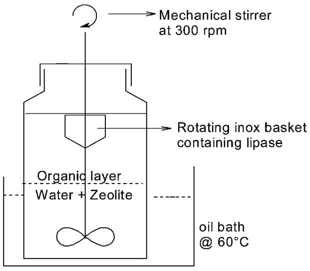


Fig. 1 Biphasic dynamic kinetic resolution reaction setup.

Table 2 Dynamic kinetic resolution of 1-phenylethanol in a biphasic system at 60 °C[a]

Entry	Organic solvent	Acyl donor[b]	Equiv. acyl donor	*t*/h	Yield (%)	ee (%)
1	octane	VA	2	2.5	18	> 99
2	octane	IPA	2	1.5	10	> 99
3	octane	VO	2	4	28	> 99
4	octane	VL	2	5	22	> 99
5	toluene	VO	2	4.5	6	> 99
6	tetradecane	VO	2	24	30	> 99
7[c]	octane	VO	2	1	40	> 99
8[c]	octane	VO	16[d]	8	90	> 99
9[c,e]	octane	VO	12[d]	6	79	> 99
10[c]	octane	OA	2	10	62	> 99
11[c]	octane	OA	10	20	74	> 99
12[c]	octane	OA	20	22	78	98

[a] Reaction conditions: 1.27 mmol 1-phenylethanol, 50 ml water, 50 ml organic solvent, air, 60 °C, 413 mg beta zeolite CP814E-22, 11 mg Novozym 435®, 300 rpm. [b] VA = vinyl acetate, IPA = isopropenyl acetate, VO = vinyl octanoate, VL = vinyl laurate, OA = octanoic acid. [c] The amount of enzyme was increased to 110 mg. [d] Acyl donor was added in portions of 2 eq. h^{-1}. [e] Second run reusing the enzyme and complete water layer with zeolite.

In addition, the re-use of the system was tested by recovering the enzyme and the complete water layer containing the zeolite. Before re-use, the water layer was extracted with octane to remove residual substrate of the previous run. The yield *vs.* time curves for the first and second runs are superimposable, indicating no deactivation of the zeolite nor of the enzyme (entry 9).

In order to avoid the hydrolysis of the acyl donors, the resolution may also be performed as a direct esterification, instead of a transesterification, adding carboxylic acid at the start of the reaction instead of vinyl esters. With the apolar octanoic acid, aselective acid-promoted esterification is avoided, and ester yields up to 78% with excellent ee_p are achieved (entries 10–12).

In summary, H-Beta-zeolites are efficient heterogeneous catalysts for benzylic alcohol racemization in water. The racemization can be combined with enzymatic kinetic resolution in a one-pot, two-phase procedure leading to yields up to 90% of enantiomerically pure ester starting from the racemic alcohol, with easy work-up.§

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Notes and references

† Ee values were determined with chiral GC (HP 6890) on a CP-CHIRASIL-DEX CB column (25 m) and FID detection.

‡ The presence of the ether dimer sideproduct was shown using GC (HP 5890A) on a CP-Sil-5 CB column (30 m) with FID or MS detection.

§ For DKR based on esterification and transesterification, the workup is similar and simple, since the mixture contains at the end only (*R*)-1-phenylethyl octanoate, octanoic acid and residual racemic alcohol substrate. After the octane layer is twice washed with 50 ml 0.6 M $NaHCO_3$, a > 99% pure solution of the (*R*)-ester (ee_p > 99%) is obtained.

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