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# Acid Zeolites as Alcohol Racemization Catalysts: Screening and Application in Biphasic Dynamic Kinetic Resolution

**S. Wuyts, K. De Temmerman, D. E. De Vos, and P. A. Jacobs*[a]**

**Abstract:** Acid zeolites were screened as heterogeneous catalysts for racemization of benzylic alcohols. The most promising zeolites appeared to be H-Beta zeolites, for which the optimal reaction conditions were studied in further detail. The zeolite performance was compared to that of homogeneous acids and acid resins under similar reaction conditions. In a second part of the research, H-Beta zeolites were applied in dynamic kinetic resolution (DKR) of 1-phenylethanol, which was conducted by means of a two-phase approach and which resulted in yields smoothly crossing the 50% border up to 90%, with an enantiomeric excess of >99%. To explore the applicability of this biphasic methodology, several other substrates were examined in the standard racemization reaction and in the biphasic dynamic kinetic resolution.

**Keywords:** biphasic catalysis · heterogeneous catalysis · kinetic resolution · racemization · zeolites

## Introduction

One of the emerging methods to obtain enantiomerically pure chiral compounds is the application of dynamic kinetic resolution (DKR), in which a resolution step, often through biotransformation, is combined in situ with a racemization step.[1–6] A large number of resolution methods has been described in the literature, comprising use of enzymes[7–10] and other, purely chemical, tools.[11] The main drawback of classical kinetic resolution (KR) is the maximum yield of 50% that can be obtained when starting from the racemic mixture. When a racemization step is integrated in the reaction, the main advantage of KR remains: one can start from the cheap racemic mixture, but the yield of 50% can be surpassed and yields of up to 100% can be achieved in one step. Moreover, depletion of the reacting enantiomer is avoided in DKR, and in this way a decrease of the enantiomeric purity of the product in the course of the reaction is circumvented.[2,12] The mechanism of racemization and the reaction conditions required depend on the stability of the stereogenic center, which is itself influenced by the functional groups on the stereogenic atom or at the α-position.[13] In many cases, racemization of a chiral substrate requires harsh conditions that are incompatible with the milder reaction conditions needed for successful resolution. Therefore, it is important to catalyze racemization so that it can proceed under milder conditions. For the racemization of chiral alcohols, transition-metal-catalyzed routes have been developed based on hydrogen-transfer mechanisms.[14–20] Recently, Maschmeyer et al. studied in detail the mechanisms of these racemization reactions, which are closely related to Meerwein–Ponndorf–Verley reduction and Oppenauer oxidation reactions (MPVO redox reactions).[21] Some racemization catalysts were successfully combined with a resolving enzyme in DKR; however, the re-use of these catalysts is not trivial, and in some resolution reactions 4-chlorophenyl acetate is used[6] instead of more convenient acyl donors, such as ethyl acetate[14b] or isopropenyl acetate.[17,20]

Alternatively, chiral alcohols, such as 1-phenyl-1-ethanol, may be racemized by means of protonation, water loss, and formation of an $sp^2$ carbenium ion, which is planar and prochiral.[22–24] Subsequent water addition is aselective and results in a racemic mixture (Scheme 1). If this Brönsted acid catalyzed racemization is performed in a water-rich medium, the elimination reaction to the alkene can be avoided. As this racemization method is especially suitable for alcohols, producing well-stabilized carbenium ions, formation of an anti-Markovnikov product, for example, 2-phenylethanol, is highly unlikely.

In line with our previous attempts to develop heterogeneous catalysts for alcohol racemization and potential applica-

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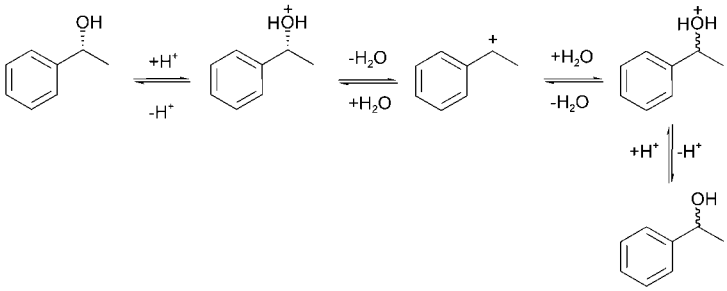



Scheme 1. Acid-catalyzed racemization of 1-phenyl-1-ethanol.

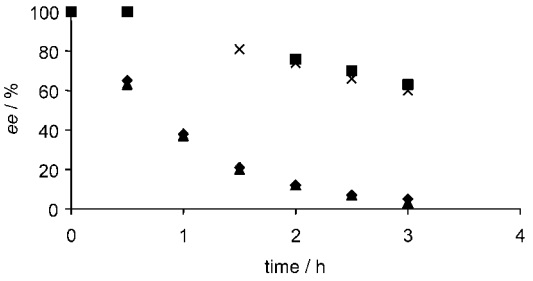



Figure 1. Racemization of 1-phenylethanol with homogeneous HCl (0.1 (■) and 0.5 M (◆)) and *p*TSA (0.1 (×) and 0.5 M (▲)) acids.

tion in DKR,[25] our attention was drawn to the use of heterogeneous acids, like zeolites, as racemization catalysts. In the patent literature, the use of Amberlyst® and Deloxan® acid resins for the racemization of benzylic alcohols has been described.[22,23] Zeolites may not only be more stable than these resins, but it is also known that hardly any acidity leaks from zeolites to an aqueous solvent; this fact makes them favourable for combination with the enzymatic reaction.

Table 1. Activity of resins in racemization of benzylic alcohols.[a]

| Entry | Resin | Support[b] | Acid group | mmol $H^+$ $g^{-1}$ | $ee_{alcohol}$ [%] after 3 h |
|---|---|---|---|---|---|
| 1 | Dowex® MWC-1 | PA | −COOH | 9.5 | 100 |
| 2 | Dowex® CCR-1 | PA | −COOH | 3.8 | 100 |
| 3 | Amberlite® IRC-50 | PM | −COOH | 10 | 100 |
| 4 | Dowex® 50X2-100 | PS | $-SO_3H$ | 4.8 | 86 |
| 5 | Dowex® 50X4-100 | PS | $-SO_3H$ | 4.8 | 65 |
| 6 | Dowex® 50X8-100 | PS | $-SO_3H$ | 4.8 | 48 |
| 7 | Amberlite® IR-118 | PS | $-SO_3H$ | 4.3 | 63 |
| 8 | Amberlyst® 15 | PS | $-SO_3H$ | 4.8 | 23 |
| 9 | Nafion® NR-50 | PF | $-SO_3H$ | 0.8 | 56 |
| 10 | Nafion® SAC-13 | PF–$SiO_2$ | $-SO_3H$ | 0.15 | 30 |

[a] Reaction conditions: 5 mL double-distilled water, 80 mg resin, 0.26 mmol (*R*)-1-phenylethanol at 60 °C under vigorous stirring. [b] PA = polyacrylate; PM = polymethacrylate; PS = polystyrene resin; PF = perfluorinated resin; PF–$SiO_2$ = perfluorinated resin dispersed on amorphous silica, 10–20 %, $>200\ m^2\,g^{-1}$.

Herein, we investigate the potential value of acid zeolites as heterogeneous alcohol racemization catalysts. Relations are established between the racemization activity of the zeolites and their structure and composition. Re-use of the zeolite catalysts is also investigated. We then present a new reaction methodology in which racemization, in seemingly "harsh, acid" conditions, is combined with a resolving biotransformation using a lipase. A preliminary account of this work has appeared previously.[24]

## Results and Discussion

### Racemization

*Homogeneous acids*: Hydrochloric acid (HCl) and *p*-toluenesulfonic acid (*p*TSA) were both tested in 0.1 and 0.5 M concentrations. As can be concluded from Figure 1, no evident difference in racemization activity could be measured between these two acids: both 0.5 M acid solutions were able to racemize the substrate to an enantiomeric excess below 5 % within 3 h.

*Heterogeneous resin catalysts*: Different classes of commercially available resins were screened in a standard racemization of (*R*)-1-phenylethanol (Table 1). The resins were based on either polystyrene (PS), polymethacrylate (PM), or polyacrylate (PA) and contained either weak carboxylic acid groups (entries 1–3) or strong sulfonic acid groups (entries 4–8). Some perfluorinated (PF) sulfonic acid resins were also tested (entries 9 and 10).

The racemization of benzylic alcohols requires an acid of sufficient strength; this explains why weak, immobilized carboxylic acids like Dowex® MWC-1, Dowex® CCR-1, and Amberlite® IRC-50 did not lead to any inversion of the alcohol configuration within 3 h (Table 1, entries 1–3), under the previously defined reaction conditions. All strong acid resins caused racemization, though a large range of activities was seen. Within the Dowex® 50 series, a clear trend of increasing activity with degree of cross linking was observed (entries 4–6, corresponding to 2, 4, and 8 % cross linking, respectively). This tendency can be explained in terms of the gel character of the polymer matrix: a less cross-linked polymer will have less accessible acid sites because of the gel properties of the polymer matrix; a more cross-linked polymer results in a more macroreticular network and makes the acid sites far more accessible for the substrate molecules. Of all the resins, macroreticular Amberlyst® 15, described earlier as a racemization catalyst in the patent literature,[23] gave the best results (entry 8). Perfluorinated acid resins gave good activity, particularly if one takes into account the small amount of acid groups per gram of material

(entry 9). The activity increased even more when the Nafion® polymer was dispersed on an amorphous silica support (entry 10).

*Heterogeneous zeolite catalysts*: The properties of the zeolite samples are summarized in Table 2. Before use, all zeolites were converted to the $H^+$ form by repeated exchange with $NH_4^+$, followed by calcination.

Table 2. Properties and origin of zeolite samples used.

| Zeolite | Topology | Si/Al ratio | Specific surface [$m^2 g^{-1}$] | Manufacturer |
|---|---|---|---|---|
| CBV 600 | FAU | 2.6 | 660 | PQ zeolites |
| CBV 712 | FAU | 5.8 | 730 | PQ zeolites |
| CBV 720 | FAU | 13 | 780 | PQ zeolites |
| CBV 760 | FAU | 30 | 720 | PQ zeolites |
| CBV 780 | FAU | 37 | 780 | PQ zeolites |
| ZM 101 | MOR | 5.8 | 480 | PQ zeolites |
| CBV 21A | MOR | 10 | 500 | PQ zeolites |
| CBV 20A | MOR | 10 | 550 | Zéocat |
| ZM 510 | MOR | 11 | 530 | Zéocat |
| CP 811BL-25 | BEA | 12.5 | 740 | PQ zeolites |
| CP 814E-22 | BEA | 11 | 680 | Zeolyst |
| CP 806B-25 | BEA | 12.5 | 730 | PQ zeolites |
| ZGO-52025 | BEA | 10–15 | >400 | Süd-Chemie |
| H-MCM-22 | MWW | 10–15 | n.d.[a] | – |

[a] n.d.: not determined.

As is evident from Figure 2a, the activity of the H-Y zeolites strongly depends on the Si/Al ratio. At low ratios (2.6, 5.8) hardly any activity can be discerned. The best results are obtained with Si-rich zeolites.

The results for mordenites were, in general, better than those for H-Y zeolites (Figure 2b). Sufficiently de-aluminated zeolites resulted in fast racemization. The fastest reactions were observed with H-Beta zeolites from various suppliers and synthesis batches (Figure 2c): the enantiomeric excess (*ee*) of the substrate steeply decreased and fell below 10% after 2 h in all cases. All H-Beta zeolite samples tested have a similar Si/Al ratio; consequently, activity differences between these zeolites were only minor. Finally, H-MCM-22 was found to display considerable activity (Figure 2c). This is not unexpected, as H-MCM-22 and H-Beta zeolites share some of the same important properties, such as small crystal size, relatively high Si/Al ratio, and affinity for hydrophobic compounds.

During racemization, no acetophenone was detected; addition of acetaldehyde to a reaction in a closed pressure vessel did not influence its reaction rate. This confirms that on acid zeolites, such as H-Beta, racemization is catalyzed by Brönsted acids and not by Lewis acids, as in the related MPVO redox reactions.[21]

Two phenomena might explain why only samples with high Si/Al ratio have appreciable racemization activity. Firstly, racemization is a strongly acid-catalyzed reaction, and it is known that the acid strength in zeolites increases with the Si/Al ratio. Secondly, the hydrophobicity of the lattice increases with the Si/Al ratio. Because racemization of the apolar substrate takes place in an excess of water, it is clear that the zeolite must be sufficiently hydrophobic so that adsorption of the benzylic alcohol is preferred over water adsorption.

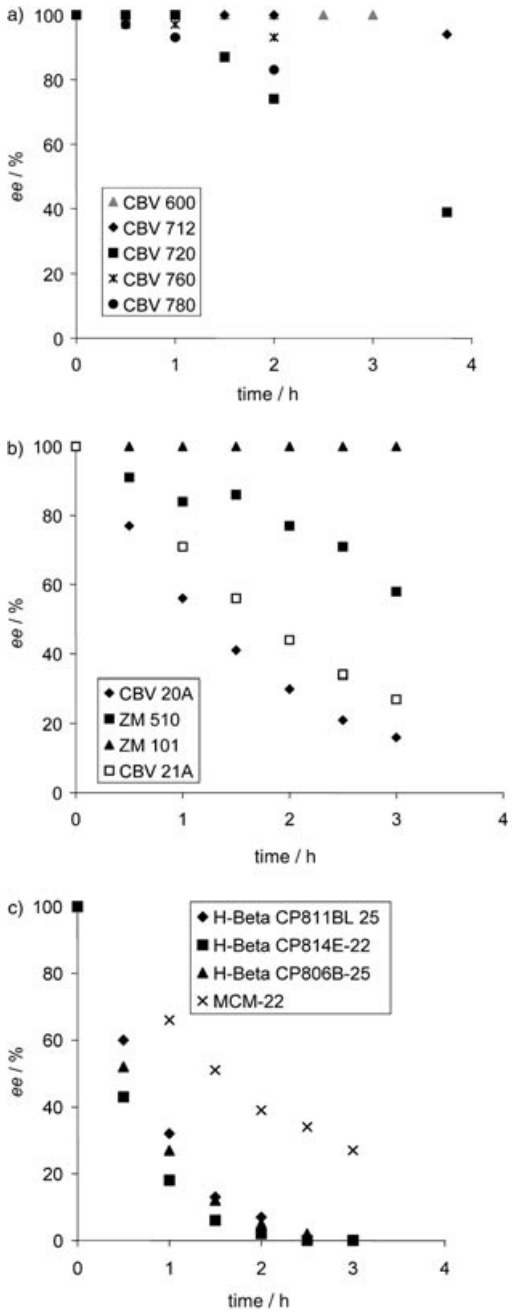
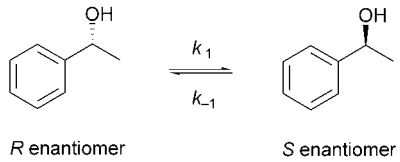



Figure 2. Racemization of (*R*)-1-phenylethanol with acid zeolites. a) H-Y zeolites, b) H-MOR zeolites, and c) H-Beta zeolites and H-MCM-22.

*Kinetics and temperature dependence of racemization*: The kinetics of the racemization reaction can be described either as the rate of interconversion of enantiomers or as the rate of formation of the racemic mixture.[26] The first approach can be described by reversible first-order kinetics as shown in Equation (1):




$$-\frac{d[R]}{dt} = k_1[R] - k_{-1}[S] \quad (1)$$

where $[R]$ and $[S]$ are the concentrations of the $R$ and $S$ enantiomers, and $k_1$ and $k_{-1}$ are the interconversion constants for the $R$ and $S$ enantiomers, respectively. Initially, when one of the enantiomers dominates the medium is chiral, and therefore, $k_1$ may differ from $k_{-1}$. In the case of a diluted solution, however, one can assume that the difference is negligible and that $k_1 = k_{-1} = k$. If the racemization reaction starts from the pure $R$ enantiomer, the elaboration of this first-order differential, with the condition $[S]_t = [R]_0 - [R]_t$, leads to Equation (2):

$$\ln\left[\frac{[R]_0}{2[R]_t - [R]_0}\right] = 2kt \quad (2)$$

where $[R]_0$ and $[R]_t$ are the concentrations of $R$ enantiomer at time zero and at time $t$, respectively. Plotting the left-hand term of Equation (2) versus time results in a straight line for the data of the zeolite H-Beta catalyzed racemization of (*R*)-1-phenylethanol (Figure 3a). The half-life $t_{1/2}$ can easily be calculated from the equation $t_{1/2} = \ln 2/2k$, in which

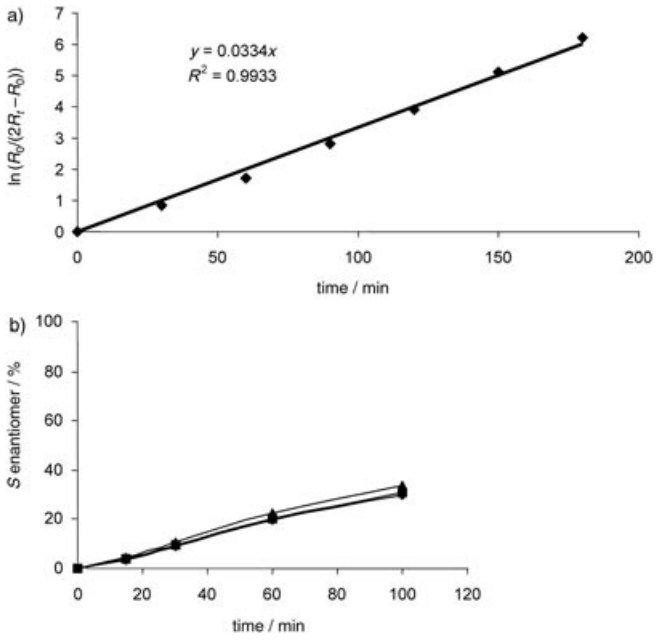



Figure 3. a) Kinetics of H-Beta-catalyzed standard racemization of (*R*)-1-phenylethanol. The straight line was fitted using Equation (2), assuming reversible first-order kinetics. b) Percentage inverted alcohol as a function of time for H-Beta-catalyzed racemization reactions with 15 (▲), 30 (■), and 45 mg (◆) (*R*)-1-phenylethanol in 10 mL water, using 80 mg H-Beta.

$t_{1/2}$ is the time required to obtain a mixture with an enantiomeric excess of 50%.

If Equation (2) is valid for racemization, plots of the percentage $S$ enantiomer formed versus time should be identical for reactions with 50 or 150% of the original amount of substrate, but using the same amount of catalyst. This can be clearly seen in Figure 3b, which proves that the assumption of a first-order rate in alcohol substrate is correct.

Additionally, the temperature dependence of racemization was investigated by screening the performance of the different racemization catalysts (0.5 M *p*TSA, Amberlyst® 15, and H-Beta) at four different temperatures (Figure 4 and Table 3). The highest activation energy ($E_a = 112$ kJ mol$^{-1}$)

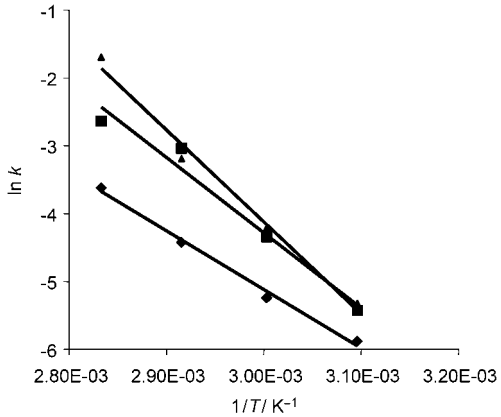



Figure 4. Arrhenius plots for the racemization of (*R*)-1-phenylethanol over acid catalysts under standard conditions. Catalysts: Amberlyst® 15 (◆), H-Beta (■), and 0.5 M *p*TSA (▲).

Table 3. Temperature dependence of racemization.

| Catalyst | $\ln k = a(1/T) + b$ | $R^2$ | $E_a$ [kJ mol$^{-1}$] |
|---|---|---|---|
| Amberlyst® 15 | $\ln k = -8642(1/T) + 20807$ | 0.9937 | 71.9 |
| H-Beta zeolite | $\ln k = -11087(1/T) + 28979$ | 0.9703 | 92.1 |
| *p*TSA (0.5 M) | $\ln k = -13531(1/T) + 36472$ | 0.9881 | 112.5 |

was obtained for the homogeneous catalyst *p*TSA. The values were lower for the H-Beta zeolite (92 kJ mol$^{-1}$) and especially for the Amberlyst® resin (72 kJ mol$^{-1}$). This indicates that for the heterogeneous catalysts, and particularly for Amberlyst®, diffusion of the reactants might slow down the overall conversion. However, the effect of diffusion on the rate seems limited for H-Beta, and the reaction is assumed to be practically under chemical control.

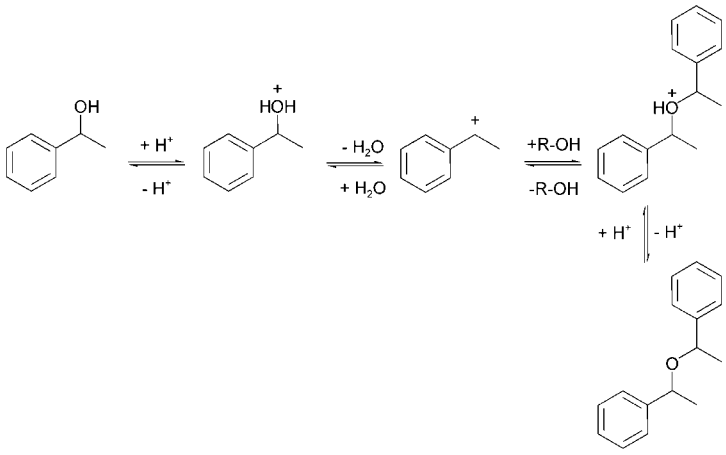
*Substrate concentration*: In order to investigate the effect of the substrate concentration on racemization, reactions using H-Beta were performed with different amounts of water (Table 4). If the substrate concentration was too high (>0.1 M), the side reaction to the 1-phenylethyl ether became important (Scheme 2, Table 4 entry 1). The dilution

Table 4. Effect of substrate concentration on racemization.[a]

| Volume of water [mL] | Substrate concentration [M] | Ether | $ee_{alcohol}$ [%] after 30 min |
|---|---|---|---|
| 2 | 0.125 | + | 24 |
| 5 | 0.05 | – | 45 |
| 8 | 0.03 | – | 55 |

[a] Reactions in water at 60 °C, 0.26 mmol (*R*)-1-phenylethanol, 80 mg of H-Beta.

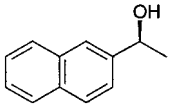
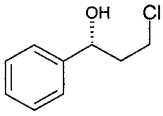
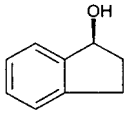



Scheme 2. Formation of 1-phenylethyl ether as a potential side reaction.

also affected the *ee* value obtained after a given time. It was evident that the reaction rate increased with the substrate and catalyst concentration.

*Substrate scope*: A number of commercially available chiral alcohols were used as the racemization substrate with H-Beta in the standard conditions developed for (*R*)-1-phenylethanol (Table 5). One of the drawbacks of the methodology is the low solubility of apolar substrates in pure water. This was definitely the case for (*S*)-1-(2-naphthyl)ethanol, which showed no racemization after extended reaction times (Table 5, entry 1). For (*R*)-3-chloro-1-phenyl-1-propanol, the substrate solubility was low but sufficient to make racemization possible (entry 2). The substrate was completely racemized within 48 h. The addition of different amounts of water-miscible co-solvents, such as acetone, 2-butanone, or acetic acid, did not result in any improvement of the reaction rate. It is likely that the increased substrate solubility was partially offset by the presence of an excess of organic molecule, which possibly adsorbed competitively on the zeolite. When ketones, such as acetone or 2-butanone, were added as co-solvents to the racemization of (*R*)-1-phenylethanol, a decrease of the reaction rate was indeed observed, which was proportional to the amount of co-solvent added (data not shown). (*S*)-2-Butanol was also screened to test the applicability of the method to simple aliphatic alcohols (entry 3); however, no racemization took place, even after extended reaction times and at an increased temperature of 80 °C.

Table 5. Racemization of chiral commercial benzylic alcohols.[a]

| Entry | Substrate | *t* [h] | $ee_{alcohol}$ [%] |
|---|---|---|---|
| 1 |  | 48 | >99 |
| 2 |  | 24 | 28 |
| | | 48 | 1 |
| 3 |  | 48 | >99 |
| 4 |  | 3 | <5[b] |

[a] Reactions in water at 60 °C, 0.26 mmol enantiopure alcohol, 80 mg of H-Beta. [b] Less than 10% of the amount of 1-indanol remained.

In the case of benzylic alcohols with electron-donating substituents, for example, 1-(4-methoxyphenyl)ethanol, or in the case of (*S*)-1-indanol, the zeolite quickly turned purple or pink, respectively (Table 5, entry 4). Similarly, formation of colored products has been described upon adsorption of 4-vinylanisole on dry Na Y, Ca Y, or Na X zeolites, or on H-Y, H-Beta, and H-ZSM-5 zeolites.[27–29] As shown in Figure 5, virtually identical UV/Vis DRS (DRS = diffuse reflectance spectroscopy) spectra can be observed when the H-Beta zeolite is exposed to 4-vinylanisole instead of 1-(4-methoxyphenyl)ethanol, and to indene instead of 1-indanol. In the case of 1-indanol, the substrate disappeared during the 24 h reaction time, and indene was formed in nearly quantitative amounts. This contrasts with all former substrates, which were not dehydrated. All of these factors indicate that the condensation in the zeolite pores probably proceeds by means of cationic intermediates (Scheme 3). In the spectrum of the zeolite reacted with 1-(4-methoxyphenyl)-ethanol, the absorptions at 368 and 580 nm have previously been ascribed to cationic intermediates.[28,29] Indene condensation on zeolites has also been described[27] with similar UV/Vis absorption maxima as in the present study. Thermogravimetric analysis (TGA) of a H-Beta zeolite exposed to 1-(4-methoxyphenyl)ethanol showed that the sample lost approximately 20% of its weight between 300 and 500 °C. This proves that the pore volume is indeed filled to a large extent with rather stable organic residues.

**Dynamic kinetic resolution**: As it is likely that racemization occurs through a Brönsted acid catalyzed mechanism, it must be performed in pure water or in a water-rich environment to avoid undesired reactions of the carbenium ion. An excess of water effectively suppresses dehydration to styrenes or ether formation (Scheme 2). On the other hand, a successful kinetic resolution requires that the enantiomerically pure product is stable, not only towards racemization, but also towards other chemical degradation reactions. The most common enzymatic resolution of alcohols is the lipase-

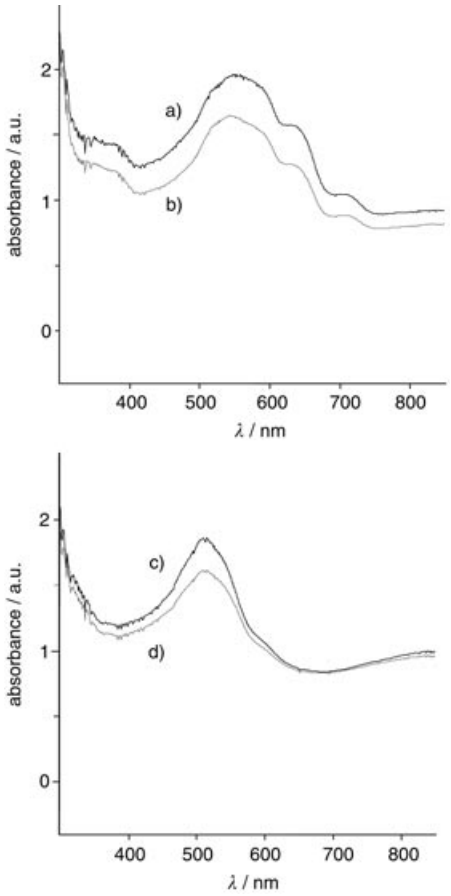
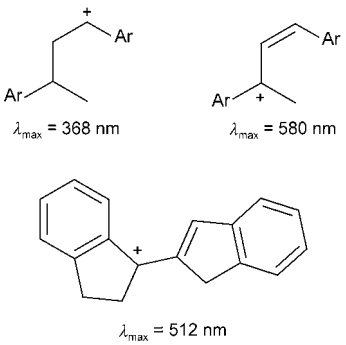



Figure 5. DRS spectra of H-Beta zeolite exposed to: a) 1-(4-methoxyphenyl)ethanol, b) 4-methoxystyrene, c) 1-indanol, and d) indene. H-Beta zeolite (1 g) in water (5 mL) was stirred overnight at 60 °C in the presence of alkene or alcohol (2 mmol).




Scheme 3. Cationic intermediates resulting from condensation reactions within the H-Beta zeolite pores.

catalyzed (trans)acylation to enantiopure esters. While these esters are not susceptible to acid-catalyzed racemization, they are easily hydrolyzed in a water-rich environment, as the lipase also accelerates the reverse-hydrolytic reaction. To physically separate racemization in the aqueous medium from the resolution reaction in the non-aqueous medium, a biphasic water/apolar solvent system was used.

In a biphasic reaction, the concentration of the substrate in either phase affects the rates of racemization and esterification. Therefore, the partitioning behavior of 1-phenylethanol was quantified by comparison with the internal standard tetradecane, which completely resides in the apolar layer. Various parameters, such as presence of the zeolite catalyst or the concentration of the acylating agent, were investigated (Table 6). The addition of H-Beta zeolite to the biphasic

Table 6. Distribution of 1-phenylethanol over the biphasic system.[a]

| Octanoic acid equiv | Zeolite[b] | Substrate in organic phase[c] [%] |
|---|---|---|
| – | – | 80 |
| – | + | 58 |
| 10 | – | 88 |
| 20 | – | 94 |
| 20 | + | 87 |

[a] Reaction system at 60 °C containing 50 mL water, 50 mL octane, 775 mg 1-phenylethanol, and internal standard. [b] 155 mg of H-Beta zeolite. [c] Measurement after complete equilibration (>1 h stirring at reaction temperature).

system resulted in an increased residence of the substrate in the aqueous layer, probably due to adsorption of the substrate on the zeolite. Conversely, addition of 10 or 20 equivalents, corresponding to approximately 2 or 4 mL, respectively, of an apolar acid such as octanoic acid resulted in an increased dissolution of 1-phenylethanol in the organic layer. In all cases, the reaction products, namely, acetyl, octanoyl, and lauryl esters, were exclusively present in the organic layer due to their pronounced apolarity. Hence, an easy product separation was possible.

The efficiency of the mass transfer of the substrate between the two layers was investigated in the following representative experiment: a 0.37 M HCl solution (50 mL) and octane (50 mL), containing an internal standard, were introduced into the reactor and brought to 60 °C. Subsequently, 1-phenylethanol (775 mg) was introduced into the upper layer, and the amount of 1-phenylethanol in the upper layer was monitored as a function of time under stirring at 300 rpm (Figure 6). An equilibrium concentration was reached within one hour. An additional indication of efficient mass transfer was the small difference between the *ee* values of the alcohol substrate in the water and organic

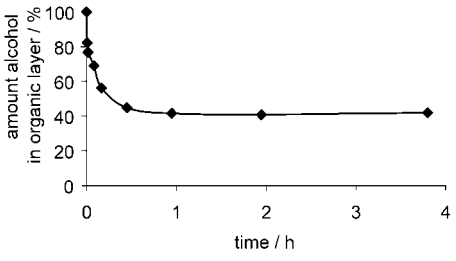



Figure 6. Representative distribution of 1-phenylethanol over the biphasic system as a function of time. Conditions: 775 mg 1-phenylethanol, 50 mL of 0.37 M HCl solution, 50 mL octane, 60 °C.

layers during DKR. In the water layer the *ee* was lower due to the ongoing racemization, but the difference between it and the *ee* of the substrate in the organic layer was less than 5% for all dynamic kinetic resolution measurements performed.

*Effect of the acyl donor*: Apart from the choice of the organic solvent, the most important parameter in biphasic dynamic kinetic resolution is the choice of the acyl donor. One may choose either (activated) esters or carboxylic acids as the acylating agents; in these cases, the resolution is either a transesterification or an esterification.

In enol esters, the leaving group is an unstable alcohol that tautomerizes to a ketone or an aldehyde. These enol esters are commonly used as acyl donors in kinetic resolution reactions to shift the equilibrium of the esterification to completion. The use of 1-ethoxyvinyl esters, which has recently been reported, is based on a similar principle, with ethyl acetate as a byproduct.[30] In Table 7 the different vinyl esters that were applied in biphasic DKR are represented, together with the maximal yield obtained when acyl donor (two equivalents) was added at the start of the reaction (entries 1–4). Clearly, in the biphasic system the enol ester was susceptible to enzyme- or zeolite-catalyzed hydrolysis. Apolar enol esters, such as vinyl octanoate (VO), prefer to reside in the octane layer (approximately 85%, depending on the reaction conditions) and are therefore less susceptible to zeolite-catalyzed hydrolysis. Consequently, yields of the desired ester product were higher with VO than with vinyl acetate (VA) or isopropenyl acetate (IPA).

Table 7. Dynamic kinetic resolution with enol esters as acylating agents.[a]

| Entry | Acyl donor | log*P*[b] | Acyl equiv | *t* [h] | Enzyme amount [mg] | Yield [%] | $ee_{ester}$ [%] |
|---|---|---|---|---|---|---|---|
| 1 | vinyl acetate (VA) | 0.58 | 2 | 2.5 | 11 | 18 | >99 |
| 2 | isopropenyl acetate (IPA) | 0.94 | 2 | 1.5 | 11 | 10 | >99 |
| 3 | vinyl octanoate (VO) | 3.59 | 2 | 4 | 11 | 28 | >99 |
| 4 | vinyl laurate (VL) | 5.80 | 2 | 5 | 11 | 22 | >99 |
| 5 | vinyl octanoate (VO) | 3.59 | 10 | 24 | 110 | 74 | 98 |
| | | | | 48 | | 80 | 98 |
| 6 | vinyl octanoate (VO) | 3.59 | 20 | 24 | 110 | 73 | 98 |
| | | | | 48 | | 81 | 98 |
| 7 | vinyl octanoate (VO) | 3.59 | 16[c] | 8 | 110 | 90 | >99 |

[a] Reaction conditions: 1.27 mmol 1-phenylethanol, 50 mL water, 50 mL octane, air atmosphere, 60°C, 413 mg H-Beta zeolite CP814E-22, Novozym® 435, acyl donor added at the beginning of the reaction. [b] Calculated values using IA_*LogP*® predictor (available at http://www.logp.com). [c] 2 equiv $h^{-1}$ VO.

When the amount of VO was increased to 10 or 20 equivalents (together with the amount of enzyme), yields of up to 73 or 81% could be achieved within 24 and 48 h, respectively (Table 7, entries 5 and 6). Increasing the VO excess from 10 to 20 equivalents seemed to have a negligible effect; moreover, the VO was completely hydrolyzed after 2 and 3 h, respectively. As the hydrolysis of these enol esters leads to the formation of carboxylic acids, the ongoing resolution reaction changes from a transesterification into an esterification. Therefore, the use of these acids as acylating agents in DKR was also considered. Of course, the reaction is then limited by equilibrium, but this equilibrium can be shifted to the right by using an appropriate excess of the acid.

The use of acetic acid (AA), which was attempted first, was not successful (Table 8, entry 1). The high concentration of acetic acid in the water probably facilitated the aselective acid-catalyzed esterification, and thus led to low *ee* values for the ester product. Moreover, the presence of a large amount of acetic acid (20 equivalents equals 1.45 mL) also increased the water content of the organic layer and thus favored the ester hydrolysis, with the direct consequence of a low overall yield. When the $C_2$ acid, with a log*P* = −0.44, was replaced with a more apolar reagent such as octanoic acid (OA, log*P* = 2.68), the *ee* was very high (≥98%), indicating that the acylation was nearly exclusively catalyzed by the enzyme in the upper layer. Between 2 and 20 equivalents of the carboxylic acid were added at the start of the reaction (Table 8, entries 2–5). With acid additions of five equivalents and more, the eventual yields were well above 50%, proving that DKR, with coupled racemization and resolution, has indeed proceeded.

When comparing the activated esters to the acids as acyl donors, it was seen that DKR was faster with addition of the enol ester at a rate of 2 equiv $h^{-1}$ than the reactions with octanoic acid (Table 7, entry 7 versus Table 8). However, when the ester was completely added at the beginning of the reaction, no profit concerning yield, reaction time, or enantioselectivity was gained with respect to the use of the corresponding acid. In this context, the acid is preferred because it is much cheaper. By contrast, when VO was added in portions of 2 equiv $h^{-1}$, a fast and high-yielding DKR re-

Table 8. Dynamic kinetic resolution reactions with carboxylic acids as acylating agents.[a]

| Entry | Acid[b] | Acid equiv | *t* [h] | Yield [%] | $ee_{ester}$ [%] |
|---|---|---|---|---|---|
| 1[c] | AA | 20 | 24 | 18 | 10 |
| | | | 48 | 21 | 4 |
| 2 | OA | 20 | 5.5 | 69 | >99 |
| | | | 22 | 78 | 98 |
| 3 | OA | 10 | 5.5 | 68 | >99 |
| | | | 22 | 74 | >99 |
| 4 | OA | 5 | 5.5 | 24 | >99 |
| | | | 22 | 54 | >99 |
| 5 | OA | 2 | 22 | 28 | >99 |

[a] Reaction conditions: 50 mL water, 50 mL octane, 1.27 mmol 1-phenylethanol, 413 mg H-Beta zeolite CP814E-22, 110 mg Novozym® 435, 60°C. [b] AA = Acetic acid, OA = octanoic acid. [c] Reaction performed under identical conditions, but with 6.35 mmol substrate.

action was achieved: a yield of 90% (>99% *ee*) could be reached within 8 h after the addition of 16 equivalents of VO in total (Table 7, entry 7).

*Effect of the organic solvent*: As explained before, it is imperative to use a water-immiscible solvent in biphasic DKR, in order to perform the enzyme-catalyzed resolution in the absence of water. The solvents toluene, octane, and tetradecane were investigated, using just two equivalents of vinyl octanoate as the acyl donor. These solvents have different log*P* values, and water and the alcohol substrate are expected to dissolve to a varying extent in them. As can be seen in Table 9, the use of toluene resulted in a poor yield. This is probably due to the relatively high water content of saturated toluene, and results in hydrolysis of both the acyl donor and the ester product. Switching to the more apolar octane or tetradecane resulted in substantially higher yields. However, in tetradecane the reaction was much slower while the yield was not significantly increased (Table 9, entry 3).

Table 9. Effect of the solvent on DKR of 1-phenylethanol.[a]

| Solvent | log*P* | Reaction time [h] | Ester yield [%] | $ee_{ester}$ [%] |
|---|---|---|---|---|
| toluene | 2.7 | 4.5 | 6 | >99 |
| octane | 4.76 | 4 | 28 | >99 |
| tetradecane | 7.14 | 24 | 30 | >99 |

[a] Reaction conditions: 1.27 mmol 1-phenylethanol, 50 mL water, 50 mL organic solvent, air atmosphere, 60°C, 413 mg H-Beta zeolite CP814E-22, 11 mg Novozym® 435, 2 equiv VO at $t=0$ h.

*Amounts of enzyme and zeolite*: For successful DKR, the resolution rate should never exceed the racemization rate too much, to avoid depletion of the resolved enantiomer; this could result in an *ee* decrease of the ester reaction product.[2,12] Therefore, the amounts of zeolite and enzyme must be well adjusted while keeping the overall rate at an acceptable level.

The impact of the amount of enzyme is shown in Table 10 (entries 1–3). As can be seen, an increase from 11 to 110 mg resulted in a remarkable improvement of the ester yield and *ee* (entries 1 and 2). Control experiments showed that the enzyme was only responsible for a minor fraction of the acyl donor hydrolysis, while the major part of the acyl donor was lost through zeolite-catalyzed hydrolysis. Hence, an increased amount of enzyme does not lead to substantial loss of acyl donor, and results in a much faster overall resolution. Increasing the amount of enzyme to 220 mg did not further improve the yield (entry 3).

As the amount of zeolite affects the racemization rate, a changing zeolite concentration also influences the evolution of the substrate *ee* during DKR. After a few hours, the substrate *ee* became stationary; this stationary *ee* value was higher in reactions with less zeolite. The ester yield depends on the zeolite concentration in a complex way. When IPA was used, the zeolite evidently catalyzed the undesired hydrolysis of the acyl donor, and this effect was expected to decrease the ester yield. On the other hand, when IPA was used as the acyl donor in the presence of a large amount of zeolite, a lot of acetic acid became available by hydrolysis of the IPA, and this resulted in spontaneous formation of both the (*R*)- and (*S*)-ester. This explains why the yield was more or less constant, but the ester *ee* decreased when the amount of zeolite was increased (Table 10, entries 4–7).

When VO was used as the acyl donor, aselective transesterification was reduced to a minimum. This allowed the use of a larger amount of zeolite to keep the *ee* of the substrate at a low level and to preserve a high product *ee* (Table 7, entry 7).

*Reaction temperature*: As DKR comprises two different reactions with a different response to temperature, it is likely that there exists an optimal temperature for the overall DKR. According to the supplier, the lipase displays an optimum activity in the range of 40–60°C combined with a high value for the enantiomeric ratio *E*. However, it is unclear how fast the enzyme deactivation is. Literature indicates that a reaction temperature of 60°C should not result in enzyme denaturation.[31] Furthermore, the temperature will affect other phenomena, such as substrate distribution and diffusion, and also the side reactions. Biphasic DKR reactions were performed at 50, 60, and 80°C, and the corresponding yields and *ee* values were compared. As expected, the racemization reaction was fastest at the highest temperature, resulting in a consistently low(er) *ee* value during the whole reaction. On the other hand, the temperature dependence of the yield was influenced by the resolution method. In the case of transesterification with VO (added at 2 equiv $h^{-1}$), the highest yield was obtained at 60°C (Figure 7a and b). On the other hand, with octanoic acid as the acylating agent (ten equivalents at $t=0$), the yield was highest for $T=80$°C (Figure 7c and d). In all reactions of Figure 7, the *ee* of the 1-phenylethyl octanoate product was >99%. In summary, the absence of a clear pattern is probably

Table 10. Effect of the amount of enzyme and zeolite.[a]

| Entry | Enzyme amount [mg] | H-Beta zeolite amount [mg] | *t* [h] | Acyl donor | Yield [%] | $ee_{ester}$ [%] | $ee_{alcohol}$ [%] |
|---|---|---|---|---|---|---|---|
| 1 | 11 | 413 | 3 | VO | 22 | 96 | 17 |
| 2 | 110 | 413 | 3 | VO | 68 | >99 | 43 |
| 3 | 220 | 413 | 3 | VO | 60 | >99 | 44 |
| 4 | 110 | 413 | 8 | IPA | 69 | 75 | 22 |
| 5 | 110 | 207 | 8 | IPA | 61 | 78 | 29 |
| 6 | 110 | 104 | 8 | IPA | 69 | 82 | 41 |
| 7 | 110 | 52 | 8 | IPA | 70 | 89 | 63 |

[a] Reaction conditions: 1.27 mmol 1-phenylethanol, 50 mL water, 50 mL octane, air atmosphere, 60°C, H-Beta zeolite CP814E-22, Novozym® 435, 2 equiv $h^{-1}$ acyl donor.

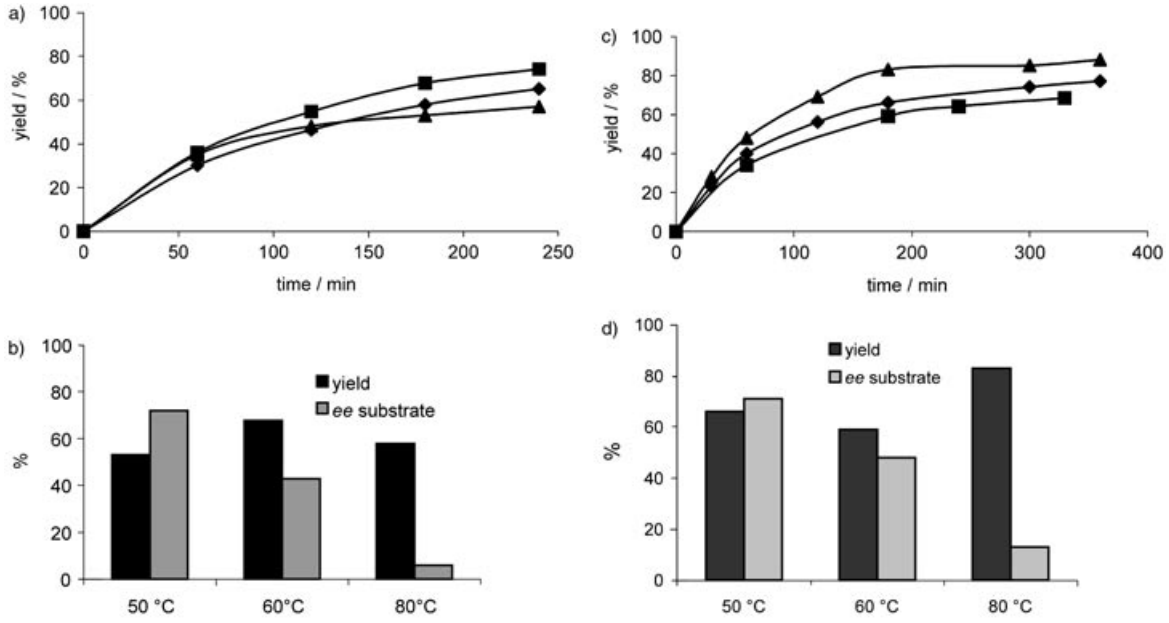



Figure 7. Effect of temperature on DKR. Yield = yield of (*R*)-1-phenylethyl octanoate. Reaction conditions for a) and b): 1.27 mmol 1-phenylethanol, 50 mL water, 50 mL octane, air atmosphere, 413 mg H-Beta zeolite CP814E-22, 110 mg Novozym® 435, 2 equiv $h^{-1}$ vinyl octanoate. Temperatures in a): 50 (▲), 60 (■), and 80 °C (◆). Reaction conditions for c) and d): 1.27 mmol 1-phenylethanol, 50 mL water, 50 mL octane, air atmosphere, 413 mg H-Beta zeolite CP814E-22, 110 mg Novozym® 435, 10 equiv octanoic acid. Temperatures in c): 50 (◆), 60 (■), and 80 °C (▲). Data in b) and d) taken after 3 h.

due to the number and complexity of the reactions and phenomena involved.

*Reaction upscale, product isolation, and re-use*: To evaluate the usefulness of the system for synthesis on a gram scale, the concentration of the substrate 1-phenylethanol was increased fivefold, together with the amounts of zeolite and enzyme. VO was added as an acylating agent at a rate of 2 equiv $h^{-1}$. After 8 h, a maximum yield of 77% was obtained ($ee_{ester} = 99\%$). In the next attempt, the substrate concentration was again increased by five times (0.127 M, 0.775 g), but the amounts of enzyme and zeolite were kept equal, and the acylating agent was octanoic acid. This resulted in a yield of 80% after 96 h ($ee_{ester} = 95\%$). This DKR was repeated without the tetradecane internal standard, enabling isolation of the pure reaction product. After removal of the zeolite-containing water layer, the organic layer was washed three times with a 0.6 M $NaHCO_3$ aqueous solution (50 mL) to remove the excess octanoic acid together with the residual substrate. After drying with $MgSO_4$ and solvent evaporation, an isolated yield of 72% in 95% pure (*R*)-1-phenylethyl octanoate was collected. This clearly shows that the system is also useful for syntheses on a larger, gram scale.

As the described protocol uses a heterogeneous zeolite catalyst and an immobilized enzyme, the re-use of both catalysts was attempted. After the first run, the organic layer was removed from the reactor, and the water layer was washed twice with pure octane to extract all residual substrate. A fresh solution of the substrate (155 mg, 1.27 mmol) in octane (50 mL) was added to the aqueous zeolite suspension, and the basket containing the original enzyme was mounted again in the reactor. As can be observed from Figure 8, there is no significant difference in reaction progress at any time during the reaction; both curves follow a similar course.

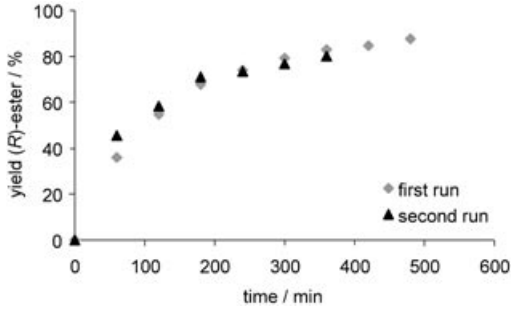
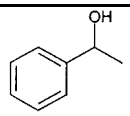
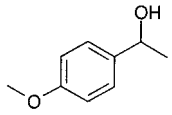
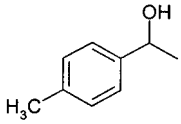
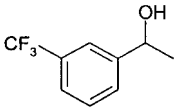
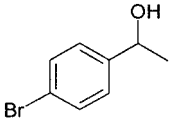
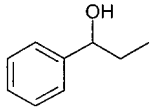



Figure 8. Re-use of the enzyme and zeolite suspension (after it was extracted to remove all residual substrate). Reaction conditions: 1.27 mmol 1-phenylethanol, 50 mL water, 50 mL octane, air atmosphere, 60 °C, 413 mg H-Beta zeolite CP814E-22, 110 mg Novozym® 435, 2 equiv $h^{-1}$ VO.

*Substrate scope*: To evaluate the scope of the new DKR, several benzylic alcohols were subjected to biphasic DKR, and the results were compared to those with the standard substrate (Table 11, entry 1). With 1-(4-methoxyphenyl)ethanol, the reaction was performed in toluene as the molecule does not dissolve in octane. Under these conditions, the yield was low and the *ee* was moderate, as might be expect-

Table 11. DKR of different benzylic alcohols.[a]

| Entry | Substrate | $t$ [h] | $ee_{substrate}$ [%] | Yield [%] | $ee_{ester}$ [%] |
|---|---|---|---|---|---|
| 1 |  | 22 | < 5 | 78 | 98 |
| 2[b] |  | 21 | –[c] | 13 | 79 |
| 3 |  | 17.5 | < 5 | 84 | > 99 |
| 4[b] | | 41 | < 5 | 66 | 94 |
| 5 |  | 74 | 62 | 39 | > 99 |
| 6 |  | 96 | 39 | 74 | 98 |
| 7[b] | | 130 | 53 | 45 | 98 |
| 8[d] |  | 70 | < 5 | 79 | 97 |

[a] Reaction conditions: 1.27 mmol racemic alcohol, 50 mL water, 50 mL octane, air atmosphere, 60 °C, 413 mg H-Beta zeolite CP814E-22, 110 mg Novozym® 435, 20 equiv octanoic acid. [b] Toluene was used as organic solvent. [c] All substrate was reacted to other species (see above). [d] Amount of enzyme increased to 330 mg.

ed, owing to the previously mentioned side reactions. After 21 h no substrate was left in the reaction (entry 2). With 1-(4-tolyl)ethanol, an enantiopure ester was obtained in yields comparable to those for 1-phenylethanol. The low substrate *ee* during the reaction indicated a smooth racemization (entry 3). For the same substrate in toluene, both yield and *ee* were decreased, in line with earlier data (entry 4). For 1-(3-trifluoromethylphenyl)ethanol, the product yield slowly approached 50% after an extended reaction time (entry 5). The substrate *ee* increased during the reaction. Comparison of ester yield and substrate *ee* indicated that the substrate was not being racemized. In that case, kinetic resolution is the only reaction going on, and the yield–substrate *ee* relation is given by $yield_{KR} = 100\,ee_{OH}/(100+ee_{OH})$.

The lack of racemization, even at 90 °C, was not due to zeolite deactivation, as zeolite isolated from this reaction was white and was still able to racemize (*R*)-1-phenylethanol. A more likely cause is that during DKR, more than 98% of the substrate resides in the organic layer, making it practically unavailable for the zeolite. Apparently, the introduction of a $CF_3$ group strongly increases the log*P* value of the substrate.

With 1-(4-bromophenyl)ethanol (Table 11, entries 6 and 7), a satisfactory yield of 74% 1-(4-bromophenyl)ethyl ester in 98% *ee* was achieved within 96 h. Compared to 1-phenylethanol, the reaction was slower; this could be due to a lower resolution rate or to a slower racemization rate, as a result of the electron-withdrawing substituent in the *para* position. The latter would translate into a continuously high substrate *ee* during the reaction. Since a true depletion of the *R* enantiomer was not observed at any point during the reaction, a slow resolution is probably the main reason for the low overall reaction rate. Yields were again lower in toluene than in octane.

Finally, 1-phenylpropanol was transformed into its octanoate by means of DKR: a yield of 79% with an enantiomeric purity of 97% was achieved after 70 h (entry 8). In order to get a smooth conversion, it was necessary to increase the amount of enzyme to 330 mg.

## Conclusions

Use of zeolites as acid catalysts for alcohol racemization were shown to be clearly superior to other heterogeneous or homogeneous acids in the racemization of (*R*)-1-phenylethanol. The best zeolite, H-Beta, was selected for an in-depth investigation of reaction conditions, kinetics, and substrate scope. Electron-rich benzylic alcohols were not suitable substrates for racemization, because of the formation of stable cationic dimers in the zeolite pores, but industrially relevant substrates, like (*R*)-3-chloro-1-phenyl-1-propanol, could be successfully racemized.

Biphasic dynamic kinetic resolution was studied in detail and optimized. This reaction used two cheap, robust, and reusable catalysts. For a series of benzylic alcohols, the enantiopure esters were obtained in yields well above 50% with excellent enantioselectivities, proving that racemization and resolution have been successfully coupled.

## Experimental Section

**Materials**: All compounds were used as-received: 1-phenylethanol (Fluka, > 98%), (*R*)-1-phenylethanol (Acros, > 99% *ee*), 1-phenyl-1-propanol (Fluka, 98%), (*R*)-3-chloro-1-phenyl-1-propanol (Fluka, 98% *ee*), 1-(*p*-tolyl)ethanol (Fluka, 97%), 4-bromo-α-methylbenzyl alcohol (Acros, 98%), 4-methoxy-α-methylbenzyl alcohol (Aldrich, 99%), 3-(trifluoromethyl)-α-methylbenzyl alcohol (Acros, 96%), (*S*)-1-indanol (Aldrich, 99%), 1-(2-naphthyl)ethanol (Aldrich, 98%), styrene (Janssen Chimica, 99%), indene (Acros, 90%), *p*-methoxystyrene (Acros, 96%), octanoic acid (Fluka, 99.5%), vinyl laurate (Fluka, > 99%), vinyl acetate (Acros, > 99%), isopropenyl acetate (Fluka, 99%), vinyl octanoate (ABCR, 98%), *n*-octane (Acros, > 99%), tetradecane (Acros, > 99%), toluene (Acros, > 99%), acetic acid (UCB, > 96%), toluene-4-sulfonic acid monohydrate (Sigma, 99%), hydrochloric acid (VEL, 37%), Nafion® NR-50 and SAC-13 (Aldrich), Novozym® 435 *Candida Antarctica Lipase B* immobilized on acrylic resin (Aldrich).

**Instrumentation**: Yields and enantiomeric purities of substrates and reaction products were determined with GC (HP 6890) on a CP-CHIRASIL-DEX CB chiral column (25 m) with FID detection. Yields were determined using tetradecane as an internal standard. The presence of the di-

meric ether side product, for example, di(α-methylbenzyl) ether, was investigated by using GC (HP 5890A) on a 30 m CP-Sil-5 CB column with FID, and a GC-MS 8000 (Fisons Instruments), equipped with a 30 m BPX5 SGE column and an MD 800 mass-spectrometer.

UV/Vis DRS measurements were performed by using a UV/Vis light source (Top Sensor Systems DH-2000 deuterium-halogen source) and a photodiode array detector (Ocean Optics SD 2000), both with optical fiber technology (Top Sensor Systems FCB-UV400-ME cable and FCG-UV400-0.1-XHT probe). For TGA measurements, a Setaram TG-DTA 92 thermobalance was employed. The sample (approximately 25 mg) was heated from 293 to 1073 K at 1 K $min^{-1}$ in a flow of helium containing 20% oxygen.

**Racemization reactions**: Racemization activities of homogeneous or heterogeneous acids in water were compared by using (*R*)-1-phenylethanol as a standard substrate.

Two dissolved acids, namely, HCl and *p*TSA, were tested in two different concentrations (0.5 M and 0.1 M). (*R*)-1-Phenylethanol (31.7 mg, 0.26 mmol) was added to the acidic solution (5 mL) in a 10 mL glass reactor and vigorously stirred (900 rpm) at 60 °C in air.

The solids tested as heterogeneous catalysts were either resins or zeolites. All materials were commercially available samples, except the H-MCM-22 zeolite, which was synthesized in-house following a standard synthesis procedure.[32] For the standard racemization tests, the resin or zeolite (80 mg) was suspended in doubly distilled water (5 mL) in a 10 mL glass reactor, and (*R*)-1-phenylethanol (31.7 mg, 0.26 mmol) was added. Although the substrate was only sparingly soluble in pure water at room temperature, the solubility seemed to be sufficient under reaction conditions. The reaction mixture was heated to 60 °C in air while being vigorously stirred (900 rpm).

**Biphasic DKR reactions**: The reaction set-up consisted of a 100 mL glass batch reactor containing water (50 mL) and a water-immiscible solvent (50 mL) with a density $<1$ g $cm^{-3}$. A stirring rotor was installed in the water layer and rotated at 300 rpm. This ensured dispersion of the zeolite in the water layer and mass transfer of the substrate between the two layers at a sufficient rate without turbulent mixing of the two phases; hence, the water–organic interphase remained clearly observable. A truncated-conical basket, containing the immobilized enzyme, was mounted on the rotating shaft at an appropriate height to be totally immersed in the upper organic layer without contact with the lower water layer (Figure 9).

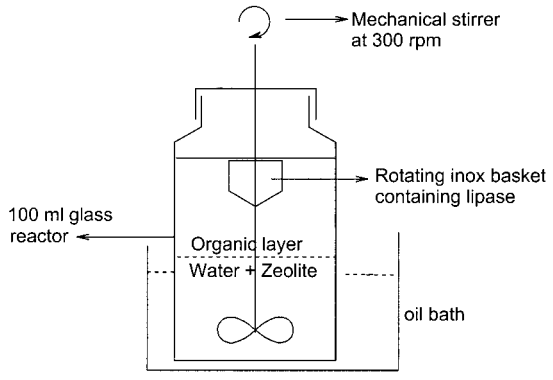



Figure 9. Biphasic reaction set-up.

Unless mentioned otherwise, typical reaction conditions were: 1-phenylethanol (155 mg, 1.27 mmol), doubly distilled water or aqueous acid (50 mL), organic solvent (50 mL), 60 °C, H-Beta zeolite (413 mg), and Novozym® 435 lipase (11 or 110 mg, corresponding to 138 or 1375 propyl laurate units, respectively). Products added during the reaction, for example, the acyl donor, were introduced into the upper layer. Novozym® 435 was chosen as it displays excellent activity and enantioselectivity in the resolution of 1-phenylethanol,[33] and because it is commercially available as small particles (in the range of 0.3–0.9 mm). The basket was made of inox gauze with a pore diameter of 0.15 mm; hence, the Novozym® 435 particles were well retained inside the basket. The reactor was immersed in an oil bath in such a way that the water layer was completely beneath the oil surface. Resulting internal temperatures for the organic upper layer are listed in Table 12. The slight temperature difference between the two layers was favorable for the overall reaction, because high temperatures favored the rate of racemization in the lower water layer, while they decreased the stability of the biocatalyst in the upper layer.

Table 12. Temperatures of heating bath and upper layer in the biphasic reactor.

| | | | |
|---|---|---|---|
| $T_{bath}$ [°C] | 50 | 60 | 80 |
| $T_{organic\ layer}$ [°C] | 44 | 55 | 73 |

## Acknowledgements

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