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Dynamic Kinetic Resolution of Secondary Alcohols Combining Enzyme-Catalyzed Transesterification and Zeolite-Catalyzed Racemization

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Abstract: Hydrophobic zeolite beta containing low concentrations of Zr or Al was found to be a good catalyst for the racemization of 1-phenylethanol. The formation of styrene as a side product could be minimized by reducing the metal concentration in the zeolite beta. Combined with an immobilized lipase from *Candida antarctica*, the dynamic kinetic resolution of 1-phenylethanol to the (*R*)-phenylethylester can be achieved with high yield and selectivity. The reaction was best conducted in toluene as solvent at 60 °C, with higher temperatures leading to a loss in the enantioselectivity of the formed ester. By using high-molecular-weight acyl-transfer reagents, such as vinyl butyrate or vinyl octanoate, a high *enantiomeric excess* of the product esters of 92 and 98 %, respectively, could be achieved. This is attributed to a steric effect: the bulky ester is less able to enter the pore space of the zeolite catalyst where the active sites for racemization are localized. Close to 100 % conversion of the alcohol was achieved within 2 h. If the more common acyl donor, isopropenyl acetate, was used, the enantiomeric excess (*ee*) of the formed ester was only 67 %, and the reaction was considerably slower.

Keywords: heterogeneous catalysis • kinetic resolution • racemization • zeolites • zirconium

Introduction

Enantiomerically pure compounds are increasingly in demand as building blocks for pharmaceutically active molecules. Besides the "traditional" method of racemate resolution by salt formation, other methods are gaining in importance. Transformations starting from the chiral pool of naturally occurring single enantiomers are a popular approach. Stereoselective reactions with chiral catalysts also offer access to enantiomerically pure products. "Chemical" catalysts based on chiral ligands and (mostly) noble metal centers and biocatalysts currently share this market at a ratio of about 2:1.[1] Chiral catalysts select only one enantiomer out of an enantiomeric pair for chemical transformation. Kinetic resolutions employ this to their advantage, because one enantiomer can be selectively transformed to a chiral product that is sufficiently different from the starting material, so that it can be separated with relative ease. The other enantiomer reacts much more slowly, and remains essentially unchanged. If the enantioselective synthesis of a desired compound starts with a racemic mixture, the yield will be limited to 50 %. A better yield can be achieved if the remaining off-enantiomer can be racemized, and the resulting mixture of enantiomers subjected to the reaction for a second time. If the processes of racemization and kinetic transformation of the faster-reacting enantiomer are conducted in the same pot, the combined system is referred to as "dynamic kinetic resolution". This term was coined by Noyori[2] in 1989. Dynamic kinetic resolutions offer the prospect of up to 100 % yield of the desired stereoisomer from a racemic starting material and are, therefore, very attractive in terms of atom efficiency.

Enzymes are excellent stereoselective catalysts. Since Zaks and Klibanov's landmark 1984 paper[3] on enzymatic reactions in organic solvents, their potential for organic synthesis is becoming increasingly recognized. Particularly, esterification reactions catalyzed by lipases in nonaqueous medium have been widely used for the kinetic resolution of alcohols in the form of esters. To overcome the intrinsic limitation of 50 % yield in kinetic resolution schemes, the catalytic racemization of the off-isomer has been described.[4] Initial work concentrated on stereolabile groups that racemize easily. Secondary alcohols are not stereolabile, and more

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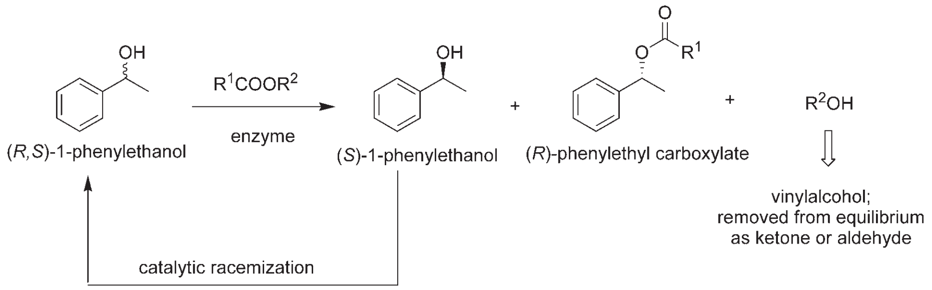
drastic conditions are required to bring about racemization. A number of homogeneous catalysts that racemize secondary alcohols under mild reaction conditions and are potentially compatible with enzymatic reactions have been described.[5] These include simple Ir, Ru, and Rh salts and also aluminium propoxide, which is active in the Meerwein–Ponndorf–Verley reduction and Oppenauer oxidation. Better rates were obtained with homogeneous catalysts comprising Ru complexes.[6] Although some difficulties with these systems have been overcome, such as the need for a strong base to form the active catalyst and the requirement for an intermediate hydrogen acceptor, they suffer from the common disadvantages of homogeneous catalysis, that is, difficulties in separating the products and regeneration of the catalyst.

Heterogeneous catalysts offer considerable advantages in processing. However, few heterogeneous catalysts for dynamic resolution have been reported. Reetz and Schimossek[7] used Pd/C for the dynamic resolution of chiral amines. Acidic ion exchangers have been used for the racemization of optically active arylethanolamines,[8] benzylic acids,[9] and acyloins.[10] Wuyts et al.[11] reported on a heterogeneous catalyst based on Ru^{3+} exchanged into a hydroxyapatite for the racemization of secondary alcohols under relatively mild conditions. However, this catalyst was not compatible with chelating groups. Even esters, which are the product of a transesterification reaction, severely deactivate the catalyst. The same group also investigated the racemization of 1-phenylethanol over a number of zeolites.[12] HY and mordenites were less active than zeolite beta. The rate of racemization increased as the Si/Al ratio increased. This was attributed to an increase in acid strength and hydrophobicity that apparently favours the adsorption of phenylethanol over that of water in the pore space of the catalyst. However, in this study, only H-beta zeolites with a Si/Al ratio of between 11 and 12.5 were investigated, and the activity of material from different sources was very similar to each other. Klomp et al.[13] found that the racemization of 1-phenyethanol occurred through elimination/addition of the hydroxyl group rather than through a Meerwein–Ponndorf–Verley–Oppenauer reduction/oxidation mechanism. They investigated zeolite beta with varying Si/Al ratios and established that the highest rate was obtained with a Si/Al of 16.



Scheme 1. Dynamic resolution of 1-phenylethanol.

The main problems faced in applying heterogeneous catalysis to dynamic resolution are a slow racemization rate and/or incompatibility of the kinetic resolution and the racemization procedures. In an attempt to resolve the latter problem, Wuyts et al.[14] carried out dynamic kinetic resolution in a biphasic system, in which an acidic H-beta zeolite catalyst suspended in the aqueous phase brings about racemization of chiral 1-phenylethanol, whereas the enzyme promotes the transesterification in the organic phase. This system appears conceptually elegant, but unfortunately, it suffers from considerable unproductive hydrolysis of the acyl donor, which must be continuously added during the reaction and reaches a 12-fold stoichiometric excess by the time the reaction is brought to completion.

Here, we report a comparison of metal-substituted beta zeolites for the racemization of (*S*)-1-phenylethanol followed by the coupling of racemization with a lipase-catalyzed stereoselective transesterification in one pot (Scheme 1). Although water can be used as the solvent for the racemization reaction, it is not suitable for transesterification. Therefore, we attempted to racemize benzylic alcohols in organic solvents over high-silica beta zeolites that were doped at a low level with other metals to generate active sites. With this class of materials, intrinsically hydrophobic catalysts were realized.

Results

Textural properties: Zeolite beta is a pentalsil zeolite with a three-dimensional network of large (12-member) rings. Beta zeolites doped with a low concentration of Sn, Ti, or Zr were synthesized by using fluoride as a mineralizer, and low-aluminium-containing beta zeolites were prepared under basic conditions with tetraethylammonium hydroxide (TEAOH) as the structure-directing agent. The physical properties of the zeolite beta prepared are given in Table 1. All the samples had surface areas in excess of 450 $m^2 g^{-1}$ and micropore volumes of 0.21–0.23 $cm^3 g^{-1}$. Regardless of the medium of synthesis, the powder X-ray diffractograms were typical for zeolite beta with both sharp and broad reflections, indicating a certain degree of disorder in one dimension. The crystallinity of all samples synthesized in the fluoride medium was higher than that of zeolite beta synthesized in basic medium (Figure 1).

The acidic properties were determined by conducting infrared spectroscopy to monitor adsorption of pyridine at room temperature and desorption at 100 °C (Figure 2). Both Sn-beta and Ti-beta show the presence of Lewis acidity with absorption bands at 1447–1460 cm^{-1}, 1488–1504 cm^{-1},

Table 1. Chemical and textural properties of zeolite beta racemization catalysts.

Catalyst	Si/Me ratio[a]		BET surface area [$m^2 g^{-1}$]	Microporous pore volume [$cm^3 g^{-1}$]	Total pore volume [$cm^3 g^{-1}$]	Water lost [%]
	Si/M	Si/Al				
Zr-beta	107	> 4000	490	0.23	0.27	1.7
ZrAl-100[a]	104	103	510	0.23	0.31	1.8
ZrAl-25[a]	105	27	533	0.21	0.24	–
Sn-beta	125	–	500	0.23	0.31	–
Ti-beta	100	–	468	0.22	0.25	0.54
Al-150	–	147	454	0.22	0.27	5.7
Al-200	–	212	241	0.10	0.18	5.6
Al-300	–	–	260	0.06	0.10	–

[a] Determined by inductively coupled plasma (ICP) analysis.

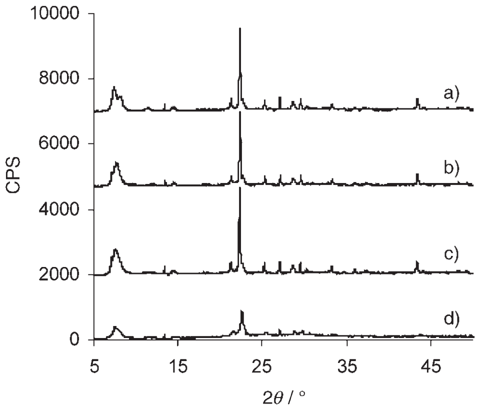


Figure 1. X-ray diffractograms of calcined a) Zr-beta, b) Sn-beta, c) Ti-beta, and d) Al-150.

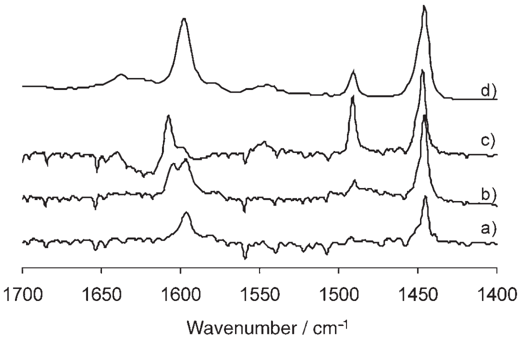


Figure 2. Pyridine absorption spectra recorded after evacuation at 100 °C for 1 h for a) Sn-beta, b) Ti-beta, c) Zr-beta, and d) Al-150.

~1580 cm^{-1}, and 1600–1633 cm^{-1} only. In contrast, the absorption band at 1540 cm^{-1}, indicative of the pyridinium ion, was detected in Zr-beta and Al-150. This band shows the presence of Brønsted-acid sites in the samples.

Thermogravimetric measurements on zeolite beta synthesized by using hydrogen fluoride (HF) indicated a weight loss of 1.7–1.8 wt % over the temperature range 100–800 °C. Results of mass spectrometry show that this weight loss is entirely due to the removal of water. Zeolite beta synthesized under basic conditions lost about 5.5 wt % over the same temperature range, indicating that these materials contain a much higher density of terminal hydroxyl groups than those prepared by using fluoride.

Racemization of (*S*)-1-phenylethanol: Sn-beta was a poor catalyst for the racemization of (*S*)-1-phenylethanol (Table 2). After 6 h, the enantiomeric excess of 1-phenylethanol was still as high as 95 %, indicating that almost no racemization occurred. In comparison, Zr-beta and Ti-beta gave moderate racemization rates. After 6 h, the enantiomeric excess (*ee*) of 1-phenylethanol was 5 % at 97 % conversion and 22 % at 79 % conversion. The selectivity to racemic 1-phenylethanol was reasonably high, 72 % for Zr-beta and 88 % for Ti-beta. Styrene is the other product formed. Incorporation of a small amount of Al into Zr-beta, as in ZrAl-100 (Si/Zr 100, Si/Al 100) reduced the racemization selectivity slightly to 70 %, whereas a higher Al content in ZrAl-25 (Si/Zr 100, Si/Al 25) resulted in a faster reaction rate, but this was offset by substantially more styrene formation.

Table 2. Racemization of 1-phenylethanol by zeolite beta synthesized with HF as mineralizer.[a]

Catalyst	Cat. wt. [mg]	Time [h]	Conversion [%]	*ee* [%]	Selectivity [%]
Zr-beta	100	6	97	5	72
Sn-beta	100	6	5.4	95	100
Ti-beta	100	6	79	22	88
ZrAl-100	100	6	96	5	78
ZrAl-25	100	2	99	3	43

[a] Reaction conditions: 0.25 mmol (*S*)-1-phenylethanol, 5 mL toluene, 60 °C.

The effect of the Al content in the zeolite beta on the phenylethanol racemization was studied further to see if an optimal balance could be reached between reaction rate and selectivity. Zeolite beta materials synthesized by using HF as a mineralizer have few connectivity defects, such as Si=O and Si−OH groups and, thus, are more hydrophobic than those formed under alkaline synthesis conditions. This is confirmed by the results of thermogravimetric analysis (TGA) that revealed a higher weight loss for Al-beta synthesized by using TEAOH than for Zr-beta for which HF was used as the mineralizer. By isotope labeling, Klomp et al.[13] showed that surface hydroxyl groups of zeolite beta participate in the hydration/dehydration of the alcohol. These groups, being acidic in nature, serve as the active sites for the racemization.

A number of Al-beta samples synthesized in a basic medium by using TEAOH were tested for their racemization activity (Table 3). Al-beta with Si/Al 150 was very active for the reaction. (*S*)-1-Phenylethanol was nearly completely racemized after only 30 min, whereas 6 h were required over Zr-beta.

Table 3. Racemization of 1-phenylethanol by zeolite beta prepared in the basic medium.[a]

Catalyst	Cat. wt. [mg]	Time [h]	Conversion [%]	*ee* [%]	Selectivity [%]
Al-12.5[b]	10	0.25	99	2	79
Al-75[c]	10	1	97	2	86
Al-150	100	0.5	98	3	61
Al-150[d]	100	0.5	97	4	60
Al-150[d]	10	0.5	98	2	84
Al-150[d]	2	1.5	92	9	90
Al-200	10	1	95	5	84
Al-300	10	6	0	100	–

[a] Reaction conditions: 0.25 mmol (*S*)-1-phenylethanol, 5 mL toluene, 60 °C. [b] Zeolyst CP814E. [c] Zeolyst CP811E-150. [d] Zeolyst CP811C-300.

However, the selectivity to racemic 1-phenylethanol was only 60 %, with the dehydration to styrene as a major side reaction. The activity of Al-150 was very similar to that of a commercial Al-zeolite beta with the same Si/Al ratio (Zeolyst CP811C-300). Reduction in the amount of Al-beta used in the racemization improved the selectivity. By using 2 mg instead of 100 mg, the selectivity to racemic 1-phenylethanol could be increased to 90 % at a threefold increase in the reaction time (Figure 3). A further decrease in the aluminium content as realized in the catalyst Si/Al 200 did not significantly improve the selectivity, but a longer reaction time was needed. For Si/Al 300, no conversion was observed even after 6 h. The results show that Zr-beta, Ti-beta, and Al-beta with low metal content are suitable candidates for application in a dynamic kinetic resolution.

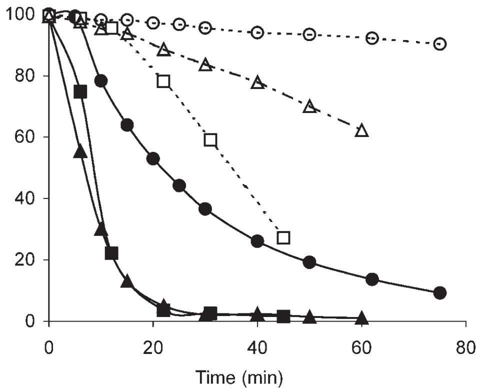


Figure 3. Enantiomeric excess (filled symbols) and selectivity (open symbols) (shown in %) of 1-phenylethanol upon racemization by (■, □) 100 mg, (▲, △) 10 mg, and (●, ○) 2 mg of Al-zeolite beta (Si/Al 150). Reaction conditions: 0.25 mmol (*S*)-1-phenylethanol, 5 mL toluene, 60 °C.

Dynamic kinetic resolution

Zr-beta: The enzyme used for the transesterification of 1-phenylethanol and isopropenyl acetate was lipase B from *Candida antarctica*, supported on an acrylic resin (commercially available under the trade name Novozym 435). Isopropenyl acetate was chosen as the acyl donor because the acetone that is liberated in the transesterification reaction is easily removed from the system. Moreover, it is compatible with the Zr-beta racemization catalyst. In experiments without the racemization catalyst, the reaction comes to a complete standstill at 50 % conversion, and the unreactive (*S*)-1-phenylethanol can be recovered in good yield and >99 % *ee*. Upon combining the racemization reaction with the lipase-catalyzed reaction, the 50 % conversion limit was exceeded after 2 h (Figure 4). After 48 h, as well as the acylated product, 1-phenylethyl acetate, two byproducts were also detected; one is styrene and the other is acetophenone. The selectivity to styrene was about 10 %. Acetophenone is formed through the Oppenauer oxidation of 1-phenylethanol, in which acetone, the leaving group of isopropenyl acetate, is the oxidizing agent. However, although Bäckvall et al.[6b] reported that with dimeric Ru(II) complex as racemization catalyst, 28 % of 1-phenylethanol was converted to acetophenone, in our experiments over Zr-beta, the selectivity to acetophenone never exceeded 1 %. This shows that racemization of (*S*)-1-phenylethanol over Zr-beta occurs by means of an elimination/hydration pathway rather than involving an Oppenauer oxidation.

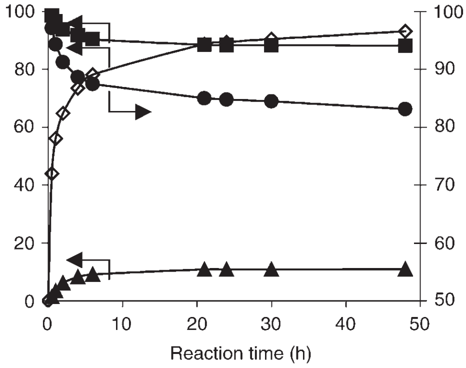


Figure 4. Dynamic resolution of 1-phenylethanol over Zr-beta. Left-hand *y* axis: (◇) conversion of 1-phenyethanol, (■) selectivity to 1-phenylethyl acetate, and (▲) selectivity to styrene (%). Right-hand *y* axis: (●) *ee* of 1-phenylethyl acetate (%). Reaction conditions: 60 °C, 1 mmol phenylethanol, 2 mmol isoproprenyl acetate, 30 mg of Novozym 435, 0.4 g Zr-beta.

As the reaction progressed, the *ee* of the product, 1-phenylethyl acetate, decreased from almost 100 % at up to 50 % conversion to about 83 % at >90 % conversion. This reduction in *ee* could be due to several reasons: 1) the selectivity of the kinetic resolution is too low so that (*S*)-1-phenylethanol is acylated as well; 2) Zr-beta catalyzes nonselective transesterification; or 3) Zr-beta racemizes the acylated product, (*R*)-1-phenylethyl acetate. The first mechanism can be ruled out, as experiments showed that Novozym 435 catalyzes the transesterification of (*R*)-1-phenylethanol at a very much higher rate than for the (*S*)-isomer. However, Zr-beta can indeed catalyze the acylation of 1-phenylethanol, albeit at a very low reaction rate. In a separate experiment, (*R*)-1-

phenylethyl acetate was slowly racemized by Zr-beta. Hence, the drop in *ee* of the product especially after long reaction times can be attributed to both the Zr-beta catalyzed transesterification of 1-phenylethanol and the racemization of 1-phenylethyl acetate.

Effect of solvents: The dynamic kinetic resolution was evaluated in several organic solvents of different polarity. The best results were obtained by using toluene as solvent, for which an *ee* value of 83 % at 93 % conversion was achieved after 48 h (Table 4). The nonpolar solvent, *n*-hexane, gave results that were almost as good; 84 % conversion and 81.6 % *ee* after the same reaction time. A high *ee* was also obtained in both 1,4-dioxane and isopropyl ether, although the conversion and yield were low due to a slow racemization rate. In the polar solvent, acetonitrile, no racemization took place and the conversion did not increase above 50 %. Presumably, the Lewis-basic acetonitrile blocks the Zr-beta sites required for the racemization reaction.

Table 4. Effect of solvents on the dynamic kinetic resolution of 1-phenylethanol over Zr-beta.[a]

Entry	Solvent	Time [h]	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	toluene	6	78	71	87.5
		48	93	82	83.1
2	*n*-hexane	6	63	59	94.3
		48	84	76	81.6
3	1,4-dioxane	6	47	40	98.4
		48	67	53	97.0
4	isopropyl ether	6	58	53	96.8
		48	69	60	92.3
5	acetonitrile	6	43	38	>99.5
		48	64	46	>99.5

[a] Reaction conditions: 60 °C, 1 mmol phenylethanol, 2 mmol isopropenyl acetate, 30 mg Novozym 435, 0.4 g Zr-beta. [b] Conversion of racemic 1-phenylethanol. [c] Yield of 1-phenylethyl acetate. [d] *ee* of (*R*)-1-phenylethyl acetate.

Effect of temperature: Temperature is another important parameter that must be optimized in performing a dynamic resolution. The racemization is usually faster at increased temperatures. However, it is frequently observed that the enzyme loses selectivity or even undergoes denaturation at higher temperatures. Moreover, additional side reactions may occur. To find the optimum reaction temperature for the kinetic resolution of 1-phenylethanol catalyzed by Zr-beta and Novozym, the reaction was studied at temperatures ranging from 50 to 80 °C (Table 5). At 50 °C, the conversion of 1-phenylethanol remained below 90 % even after 48 h. The rate of reaction was fastest at 80 °C, with more than 95 % of 1-phenylethanol converted after 24 h. However, at the elevated temperature, the *ee* of the 1-phenylethanol acetate decreased to 75 %. In Figure 5, the *ee* of (*R*)-1-phenylethanol acetate is plotted as a function of conversion. It is apparent that the enantioselectivity is somewhat higher at 50 °C and 60 °C, and decreases notably if the temperature is increased to 80 °C. Hence, 60 °C was established to be the optimum reaction temperature for this reaction system.

Table 5. Effect of temperature on the dynamic resolution of 1-phenylethanol.[a]

Entry	Temperature [°C]	Time [h]	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	50	24	84	75	84.9
		48	89	79	84.2
2	60	24	89	79	84.8
		48	93	82	83.1
3	70	6	89	76	78.4
		24	95	82	79.4
4	80	6	87	82	76.8
		24	95	81	74.9

[a] Reaction conditions: 60 °C, 1 mmol phenylethanol, 2 mmol isopropenyl acetate, 30 mg Novozym 435, 0.4 g Zr-beta. [b] Conversion of racemic 1-phenylethanol. [c] Yield of 1-phenylethyl acetate. [d] *ee* of (*R*)-1-phenylethyl acetate.

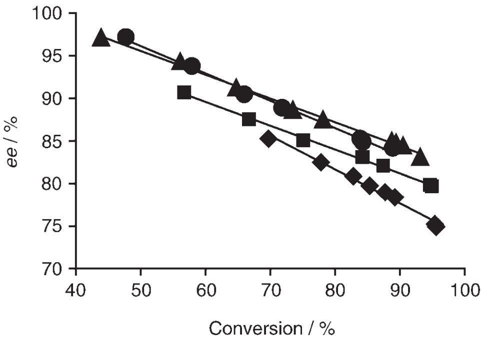


Figure 5. Dynamic resolution of 1-phenylethanol at different temperatures: (●) 50 °C, (▲) 60 °C, (■) 70 °C, and (◆) 80 °C.

Optimization of the racemization catalyst and the acyl donor: Because the racemization over Al-beta (Si/Al 150) was faster than over Zr-beta, the transesterification of 1-phenylethanol and isopropenyl acetate in the presence of lipase was carried out by using this catalyst. The racemization catalyst was added after 2 h, when the conversion had reached 50 %. The transesterification reaction resumed after addition of the racemization catalyst, and after 17.5 h, the conversion had reached 97 % (Figure 6). However, more styrene was formed, 20 %, in contrast to the 10 % formed over Zr-beta. In addition, racemization of the ester, 1-phenylethyl acetate, occurred to a greater extent so that at the end of the reaction, the enantiomeric excess was only 67 %. Hence, despite the faster racemization rate over Al-beta relative to Zr-beta, Al-beta appeared not to be an effective catalyst for the dynamic kinetic resolution of 1-phenyethanol if isopropenyl acetate was used as the acyl-transfer reagent. We reasoned that the active sites that catalyzed the racemization of the alcohol were the same as those capable of bringing about racemization of the ester. If the size of the ester molecule is increased, it should be possible to prevent its diffusion into the pore space where the active sites are lo-

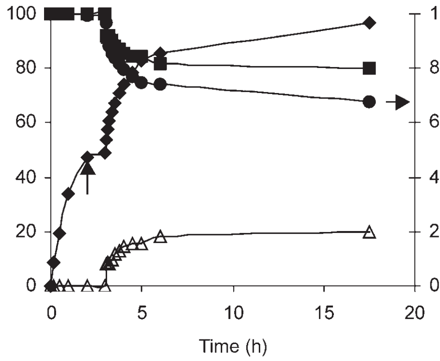


Figure 6. Dynamic resolution of 1-phenylethanol by using Al-150. Left-hand *y* axis: (◆) conversion of 1-phenyethanol, (■) selectivity to 1-phenylethyl acetate, and (△) selectivity to styrene (%). Right-hand *y* axis: (●) *ee* of 1-phenylethyl acetate (%). Reaction conditions: 1 mmol phenylethanol, 1.5 mmol isopropenyl acetate, 30 mg enzyme, 50 mg Al-150, 5 mL toluene, 60 °C.

calized, and thereby improve the enantiomeric excess of the final product.

To test this hypothesis, we carried out the transesterification reactions with the bulkier acyl donors, vinyl butyrate and vinyl octanoate (Figure 7). The racemization catalyst, Al-150, was added after 50 % conversion was reached. The rate of transesterification observed for the vinyl esters was faster than that for isopropenyl acetate, despite the bigger butyrate or octanoate group. The conversion approached 100 % within 150 min for both acyl donors, and the selectivity towards ester formation was 85–88 %. The only byproduct was styrene. The enantiomeric excess of the ester formed, phenylethyl butyrate or phenylethyl octanoate, was 92 and 98 %, respectively. This is substantially higher than for the (*R*)-1-phenylacetate formed with vinyl acetate (65 % *ee*) or isopropenyl acetate (68 % *ee*).

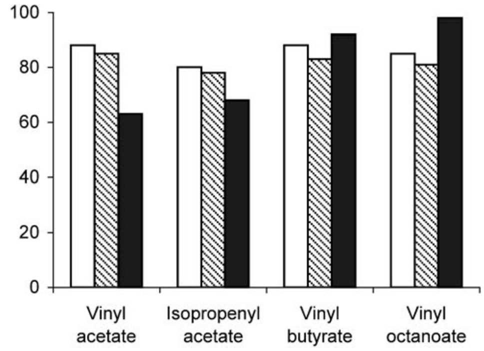


Figure 7. Dynamic resolution in the transesterification between 1-phenylethanol and various esters. The y axis represents selectivity (empty bars), yield (hatched bars), and *ee* (black bars) of the ester (%). Reaction conditions: 1.0 mmol racemic 1-phenylethanol, 1.5 mmol acyl-transfer reagent, 30 mg Novozym 435, 50 mg zeolite Al-150, 5 mL toluene, 60 °C.

Conclusion

The dynamic kinetic resolution of secondary alcohols was achieved in a single nonaqueous liquid phase in the presence of two heterogeneous catalysts. An immobilized lipase (*C. antarctica* lipase B, Novozym 435) catalyzes the stereoselective transesterification of the secondary alcohol with acyl-transfer reagents, such as isopropenyl acetate, vinyl acetate, vinyl butyrate, or vinyl octanoate, under conditions that are compatible with the catalytic racemization of the secondary alcohol over zeolite beta. Pure Si-beta or substitution with Sn gives catalysts that have almost no activity for the racemization reaction. Hydrophobic Zr-beta prepared by a hydrothermal synthesis in fluoride medium or Al-beta with a high Si content are good racemization catalysts. To create the active sites, Zr and Al have to be incorporated into the framework at a doping level of about 1 %. Styrene is formed as the major side product. Racemization catalysts with higher Al content lead to increased styrene formation.

The dynamic kinetic resolution of secondary alcohols was best carried out in a nonpolar medium, preferably toluene or *n*-hexane, rather than in a polar solvent. The optimum temperature was 60 °C. Apart from racemizing the reacted alcohol, the zeolite catalyst also caused a loss of the enantiomeric purity by racemization of the product ester. However, this could be substantially suppressed by using larger acyl-transfer reagents, such as vinyl butyrate or vinyl octanoate. The resulting bulky ester is not able to enter the active sites located in the pore channels of the zeolite catalyst and, therefore, does not undergo subsequent racemization. In this way, the (*R*)-ester can be prepared at >85 % yield and >97 % *ee*.

Experimental Section

Synthesis of Sn-, Zr-, and Ti-beta zeolites: Beta zeolites containing Sn and Zr were synthesized in a fluoride-assisted hydrothermal synthesis with the addition of seeds from dealuminated zeolite beta. Typically, tetraethylorthosilicate (TEOS) was hydrolyzed in a solution of tetraethylammonium hydroxide (TEAOH) under stirring. A solution of $SnCl_4{\cdot}5H_2O$ or $ZrOCl_2{\cdot}8H_2O$ in water was added, and the mixture was stirred until all ethanol formed by hydrolysis of the TEOS had evaporated.[15,16] Hydrogen fluoride and an aqueous suspension of seeds of dealuminated nanocrystalline zeolite beta (ca. 50 nm in diameter, as determined by TEM) were added. Crystallization was carried out in a static Teflon-lined stainless-steel autoclave at 140 °C for 25 days. The solid product was filtered, washed with deionized water, dried at 100 °C, and activated at 580 °C for 4 h. Two Al-containing Zr-beta samples, ZrAl-100 (Si/Zr ≈ 104, Si/Al ≈ 103) and ZrAl-25 (Si/Zr ≈ 105, Si/Al ≈ 27) were synthesized in an analogous way to the synthesis of Al-free Zr-beta, except for the addition of the required amounts of $ZrOCl_2{\cdot}8H_2O$ and $Al(NO_3)_3{\cdot}9H_2O$.

Ti-beta (Si/Ti ≈ 100) was prepared by following the procedure described by Blasco et al.[17] For a typical synthesis, titanium ethoxide (TEOT) (0.12 mL) was added to TEOS (10.42 g), followed by the dropwise addition of a 40 % TEAOH solution (10.31 g). To facilitate the dissolution of TEOT, H_2O_2 (30 % w/w; 1.93 mL) was added. The resulting mixture was stirred until the ethanol formed upon hydrolysis of TEOS and TEOT had completely evaporated. Hydrogen fluoride (HF) (Aldrich, 48 %, 1.014 mL) was added to the cloudy solution, whereupon a thick paste formed. Dealuminated nanocrystalline zeolite beta seeds (~50 nm, 0.105 g) in water (2.4 mL) were added. The crystallization was carried out in a Teflon-lined stainless-steel autoclave at 140 °C for 10 days.

Synthesis of Al-beta zeolites: Beta zeolites with Si/Al 75–200 were prepared according to reference [18]. Typically, aluminium metal was dissolved in TEAOH (40 wt %) followed by the addition of deionized water and fumed silica (Aerosil 200). The mixture was stirred for 2 h before being placed in a Teflon-lined stainless-steel autoclave and kept at 140 °C for 3 days under autogenous pressure. The molar composition of the final gel mixture was Al_2O_3:$x$$SiO_2$:$(0.26x+1)$$TEA_2O$:$15x$ H_2O, for which x ranged from 400 to 150. The samples are denoted Al-n, for which n stands for the Si/Al ratio (75–200).

Catalyst characterization: The surface area and porosity properties were determined by using nitrogen adsorption (Micromeritics Tristar). Prior to measurement, the samples were thoroughly degassed under a nitrogen flow for 4 h. The formation of the crystalline phase was measured by using powder X-ray diffractometry (Siemens D5005 with Cu anode and variable slits). To determine the hydrophobicity of the samples in terms of amount of water lost, the weight loss was monitored by thermogravimetric analysis (TGA) in a Dupont SDT 2960 analyzer. About 5–10 mg of sample was first dried in a flow of dry nitrogen (100 $mL\,min^{-1}$) before increasing the temperature to 800 °C at 10 $°C\,min^{-1}$.

IR spectroscopy of adsorbed pyridine was employed to determine the type of acidic sites present on the zeolites. The IR spectra were recorded by using a Bruker Equinox 55 with a resolution of 2 cm^{-1}. Typically, samples were pressed into self-supported wafers of 8–10 mg. The wafer was mounted inside a Pyrex IR cell with NaCl windows and dried under vacuum (~10^{-3} mbar) for 2 h at 300 °C. After cooling to RT, a background spectrum was recorded. Subsequently, the sample was exposed to pyridine at 22 mbar for 15 min. The pyridine was pumped off and the sample was evacuated under vacuum (~10^{-3} mbar) for 1 h before an IR spectrum was recorded. The sample was then heated to 100 °C for 1 h under vacuum to desorb loosely bound pyridine, cooled to RT, and another IR spectrum was recorded. A further measurement was taken after desorption at 200 °C.

Racemization of (*S*)-1-phenylethanol: The racemization of (*S*)-1-phenylethanol was carried out in a two-necked round-bottomed flask equipped with septum port, reflux condenser, and a guard tube. Typically, (*S*)-1-phenylethanol (0.25 mmol; $ee > 99.5$ %) was dissolved in toluene (5 mL) and heated to 60 °C. Catalyst (100 mg) was added to the reaction mixture (time = 0) Progress of the reaction and enantiomeric excess were monitored by performing gas chromatography (column: Supelco Beta Dex 325 (250 μm × 0.25 μm × 25 m); flame ionization detector). Only the two isomers of 1-phenylethanol, and the byproduct, styrene, were observed.

Dynamic kinetic resolution of 1-phenylethanol: The zeolite catalyst (50–400 mg) was added to a reaction mixture of 1 mmol racemic (*R*,*S*)-1-phenylethanol in solvent (5 mL) and Novozym 435 (30 mg). The reaction slurry was stirred and heated to the desired temperature, normally 60 °C, although temperatures of 50–80 °C were also studied. At time $t=0$, isopropenyl acetate (2 mmol) was added. The progress of the reaction was monitored by performing gas chromatography using a Supelco Beta Dex 325 chiral capillary column. The identity of the products was verified by comparing the retention times and GC/MS spectra with authentic samples. As well as isopropenyl acetate, other esters, such as vinyl acetate, vinyl butyrate, and vinyl octanoate, were also used as acyl-transfer reagents. A Supelco Beta Dex 120 column was used for separating the enantiomers of phenyl butyrate and phenyl octanoate. Close to 100 % conversion was reached after about 2 h of reaction at 60 °C.

Scale-up to a semipreparative scale: 1-Phenylethanol (1.22 g, 10 mmol) and vinyl octanoate (1.70 g, 10 mmol) were dissolved in toluene (5 mL), and Novozyme 435 (150 mg) was added after the temperature had reached 60 °C. After 2 h, zeolite beta Al-150 (250 mg) was added to the reaction mixture and the reaction was allowed to proceed for another 4 h. At completion of reaction, the solid catalysts were removed by filtration, and toluene was distilled off under reduced pressure. The product containing mainly 1-phenylethyl octanoate and side products, such as styrene and octanoic acid (due to the hydrolysis of vinyl octanoate), were redissolved in hexane (20 mL) and the octanoic acid was removed by washing with 0.6 M $NaHCO_3$ solution (3 × 20 mL). The organic layer was dried with anhydrous Na_2SO_4 and styrene and hexane were removed by vacuum distillation (1 mbar at 50 °C for 2 h). After work-up, essentially pure (*R*)-1-phenylethyl octanoate was obtained with an isolated yield of 72 % and 97.7 % *ee* (average from two runs).

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