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Catalysis Today 97 (2004) 263–270
CATALYSIS TODAY
www.elsevier.com/locate/cattod

Process intensification with biocatalysts: dynamic kinetic resolution and fluorous phase switch with continuous extraction

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Abstract

Kinetic resolution of racemates with the help of enzymes has become a widely adopted method for the synthesis of chiral intermediates and compounds with biological activity. However, the inherent limitation to 50% yield of any one stereoisomer restricts the use of this method in industrial practice, when only one of the stereoisomers is required. The yield can theoretically be improved to 100% through either a chemical reaction, which inverts the stereochemistry at the optical active center, or through racemization of the unwanted isomer, followed by additional enzymatic resolution. The combination of the racemization of the slower reacting stereoisomer with kinetic resolution in a one-pot reaction is termed dynamic resolution. We describe the dynamic resolution of secondary alcohols through enzymatic stereoselective transesterification and heterogeneously catalyzed racemization of the alcohol over several zirconia-containing catalysts. In order to facilitate the separation of the products, we used a fluorous phase-switching technique coupled with fluorous extraction. The continuous extraction in a membrane contactor allows for facile recovery of the fluorous tagged species in a scaleable operation. The unoptimized scheme offers over 90% conversion with ca. 75% enantiomeric excess (e.e.).

Keywords: Dynamic resolution; Enzymes; Fluorous phase; Membrane-assisted extraction; Zirconia

1. Introduction

Demand for enantiomerically pure compounds is increasing, driven not only by the pharmaceutical industry but also from flavors and fragrances and the food industries. The world-wide sales of single-enantiomer drugs reached almost US$ 160 billion in 2003, accounting for about 37% of all drug sales [1]. Over the last decade, single enantiomer drugs grew at an average annual rate of about 15% compared with only 8% growth for pharmaceuticals, in general. Pure enantiomers can be obtained by ''chiral pool'' synthesis, making use of naturally occurring chiral building blocks, by conventional chemical synthesis with subsequent racemate resolution, e.g., using chiral auxiliaries via diastereomer formation, by process scale chiral chromatography, or by chiral induction over chiral catalysts. Enzymes are the quintessential chiral catalysts. However, processes with enzymes have to be designed taking the specific properties of enzymes into consideration. Enzymatic reactions fall into two broad classes: kinetic resolution of racemates and stereoselective conversion of prochiral compounds into single stereoisomers. The latter path offers potentially 100% yield of the desired stereoisomer, whereas the resolution methods will achieve only 50% yield unless the undesired stereoisomer can be easily racemized and recycled [2,3].

We investigated the possibility to convert a racemic secondary alcohol completely into a single enantiomer ester by a dynamic resolution. In this process, the stereo-selective esterification is coupled with the catalytic racemization of the slow-reacting alcohol isomer in a one-pot reaction. In the pharmaceutical and food industry, special consideration has to be paid to the toxicity of all materials involved in the synthesis, in order to prevent objectionable residues in the final product. Many solvents as well as heavy metals are highly toxic. If they have been used in a synthesis, it has to be assured that they are completely removed from the final product. Perfluorided solvents are chemically inert and

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doi:10.1016/j.cattod.2004.07.008

non-toxic. We evaluate the use of fluorous phase extraction for the separation of a fluorous tagged single enantiomer from the reaction mixture in a continuous process.

During the past 20 years, enzymes have gained some acceptance as chiral catalysts within the tool kit of the organic chemist. The progress in this field has been reported in monographies [2–12] and review articles [13–16]. However, applications on a process scale are still rare because of the misperceptions and prejudices that continue to be held by many synthetic chemists, notably:

- enzymes are highly substrate specific;
- enzymes operate only in aqueous medium;
- enzymes can handle only low substrate concentrations;
- enzymes are expensive; and
- enzymes are too sensitive.

Large scale industrial enzymatic racemate resolution started in 1966 in Japan (L-amino acids; Tanabe Seiyaku) [17]. In this process, an immobilized acylase was used in a fixed-bed reactor. Since then, many more processes have been implemented using enzymes. The increasing availability of industrial enzymes plays a vital role in this development. Some enzymes are produced in large scale, particularly proteases and lipases, for use in detergents, also cellulases, amylases and others. Modern biotechnology has made it possible to over-express desired enzymes in easy to grow microorganisms, and to produce them at relatively low prize. Many enzymes have been improved in their properties to match the demands of the end-use, e.g., alkali stability and high temperature tolerance for enzymes used in laundry detergents. As such, a large variety of enzyme preparations are available to the synthetic chemist at a relatively low price. However, it remains a tedious task to identify a suitable enzyme for a specific reaction, as it is difficult to predict the activity or selectivity of a given enzyme [18]. If no suitable enzyme can be found strategies such as mutagenesis and directed evolution [19] are required to increase the activity and selectivity.

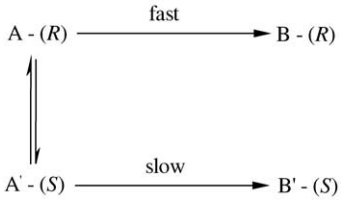
Lipases (glycerin hydrolases) accept a wide variety of substrates, including secondary and primary alcohols and their esters, amines, and amides. Since the seminal publication of Zaks and Klibanov [20] in 1984, it has been realized that enzymes are not restricted to aqueous medium, but can also be used in organic solvents to great advantage [21]. This overcomes many problems with substrate solubility, and the use of immobilized enzymes in organic solvents frequently extends their useful temperature range to above 70 °C.

1.1. Kinetic resolution

Kinetic resolution makes use of the fact that an enzyme often accelerates the reaction with one stereo-isomer much more than with the other. In the ideal case, the faster isomer is quantitatively transformed into a product, whereas the other one remains unchanged. If the product differs in some properties sufficiently from the starting material, separation becomes unproblematic. The enantiomeric excess (e.e.) is a function of conversion and the kinetic ratio *E*. The relationship between e.e., *E*, and conversion has been derived by Noyori and co-workers [22]. Obviously, the maximum yield of the desired isomer cannot exceed 50% of the racemate unless the off-enantiomer can be used. This becomes possible if the stereochemistry of the pure isomer can be inverted, e.g., under Mitsunobu conditions [23–25].

Another possibility is to couple the resolution with the isolation and subsequent racemization of the off-isomer, which can then be recycled and again subjected to resolution. This process can be executed sequentially, in which case five stages will lead to 97% yield if the theoretical limit of 50% can be realized in each step [26]. It is more economical if the racemization of the unconverted isomer and recycling into the resolution stage can be done in a continuous process (Scheme 1). For such a process, the term ‘‘dynamic (kinetic) resolution’’ has been coined. The concept of dynamic resolution in homogeneously catalyzed hydrogenations has been demonstrated by Noyori et al, [27,28] and others (Scheme 1).

Dynamic resolutions involving enzymatic reactions have also been described. Bäckvall and co-workers [29–34] reported the stereoselective conversion of γ-hydroxy acid derivatives with lipase and a ruthenium-catalyzed racemization under mild conditions (60–70 °C, 4 h; up to 93% conversion and 98% e.e.). Similar schemes, using mostly Ru-based catalysts, have been described by other groups [35–38]. Secondary alcohols are conformationally stable. However, racemization can be brought about by either acid catalysis, probably involving the dehydration–hydration sequence, or in a redox scheme via intermediary formation of the ketone. We have previously studied the heterogeneously catalyzed Meerwein–Ponndorf–Verley reduction and Oppenauer oxidation (MPVO reaction) over zeolites and hydrated zirconia [39,40]. The MPV-reduction involves hydrogen transfer from an easily oxidized alcohol to a ketone or aldehyde. i-propanol is preferred as hydrogen donor because the corresponding oxidized product, acetone, is volatile and readily removed from equilibrium. However, if both the alcohol and ketone remain in the reaction mixture, one will reach equilibrium. This can be used as advantage to bring about the racemization of a secondary alcohol. A similar method has recently been reported by Wuyts et al. [41,42]. The strategy of our work is to develop a



Scheme 1. Principle of dynamic kinetic resolution.

dynamic kinetic resolution, which uses a simple heterogeneous catalyst together with an immobilized enzyme.

1.2. Fluorous phase switch

It is a severe drawback of many kinetic resolutions that the separation of the reaction products requires chromatography. While chromatographic techniques are highly developed and allow for almost any separation at a laboratory scale, they are not easily scaled to production. We, therefore, attempted to develop a scaleable process for a kinetic resolution with fluorous tagging, coupled with a continuous extraction process. Curran [43] pointed out the importance to integrate the separation in the synthesis, and reviewed the merits of fluorous solvents for fluorous extraction. Perfluorided or highly fluor-containing solvents are insoluble with water as well as with many organic solvents. This offers interesting combinations for selective extraction systems. Barthel–Rosa and Gladysz [44] discuss the properties of fluorous systems and provide much useful information on distribution coefficients and physical properties. Fluorous solvents should offer several advantages: the high specificity in extracting only 'fluorous' compounds, coupled with low heat of evaporation, wide liquid range, essential non-flammability, chemical inertness, and low toxicity. Fluorous solvents are not defined by the US EPA as volatile organic compounds. On the downside, these solvents are very expensive, and recently, some doubt arose with respect to their perceived non-toxicity. Because of the extremely low water solubility and high volatility, fluorous solvents will exclusively partition into the atmosphere. Here, the atmospheric life-time is extremely long (more than 1000 years). The compounds have zero ozone depletion potential, but a very high greenhouse potential of about 5000 times that of CO_2. Any viable process has, therefore, to be designed in such a way that emissions of the fluorous solvents into the environment are minimized.

Theil and co-workers developed a new acylation reagent, trifluoroethyl-1*H*,1*H*,2*H*,2*H*-perfluoroundecanoate [45–47], and demonstrated its compatibility with lipase-catalyzed transesterifications. Compounds that had been tagged with this fluorous 'ponytail' could be easily extracted into a fluorous solvent (perfluorohexane; FC-72). They also proposed an ingenious three-phase system for continuous extraction [48]. The distribution coefficients for fluorous tagged compounds between an organic and a fluorous solvent depend on the fluorine content (H/F ratio) of the molecule; however, even for a high H/F ratio of 0.75, the partition coefficient K_P is in the order of unity. We measured a value of about 2 for the distribution of 1*H*,1*H*,2*H*,2*H*-perfluorodecanol in the system methanol/perfluorous solvent, independent of the fluorous solvent used. Multiple extraction steps are therefore necessary to quantitatively recover the fluorous compounds. We discuss a continuously operating membrane-assisted extraction, similar to that recently described by Baudot et al. [49] for the extraction of flavor compounds from aqueous solutions into olive oil.

2. Experimental

The fluorous acyldonor 2′2′2′-trifluoroethanol 1*H*,1*H*,2*H*,2*H*-perfluorundecanoate (**1**) was synthesized in 4 steps, starting from commercially available 1*H*,1*H*,2*H*,2*H*-perfluorodecanol, following the procedure developed by Theil and co-workers [45,46]. A number of immobilized and lyophilized lipases were used in this study; some of their properties are given in Table 1. Most enzymatic reactions were done in glass vials with septum closure, through which samples were withdrawn at intervals for analysis. Larger-scale experiments were done in conventional laboratory equipment under argon. In a typical exploratory experiment, 0.174 mmol of perfluoroester 1 and 0.116 mmol rac. 1-phenylethanol were dissolved in 1.5 ml of a selected solvent in a microvial and stirred at 45 °C using ca. 20 mg of the enzyme. Conversion was followed by gas chromatography (HP-5 column, (5% Phenyl)-methylpolysiloxane). The enantiomeric excess was determined either by chiral gas chromatography (Betadex 325, Supelco) or HPLC (Chiralcel OD-H, Daicel; isocratic, 95% hexane/isopropanol, flowrate 1 ml/min). For work-up, the enzyme was filtered off, the organic solvent evaporated, and the residue taken up in methanol. The methanol phase was extracted 8 times with equal volumes of the fluorous solvent. The fluorous compounds (fluorous tagged (*R*)-1-phenyl ethanol and unreacted **1**) were saponified with LiOH. The (*R*)-1-phenylethanol could be easily separated from the solid Li salt of the 1*H*,1*H*,2*H*,2*H*-perfluoroundecanoic acid.

Table 1
Properties of lipase preparations

Lipase	Specific activity[a] (U/mg)	Activity[b] (μmol/g h)	Form of preparation	Supplier
Pseudomonas fluorescens	0.061	50.9	Immobilised in Sol–gel–AK	Fluka
Porcine pancreatic	147	7.3	Lyophilized powder	Sigma-Aldrich
Rhizomucor miehei (Lipozyme®)	0.007	27.6	Immobilised on Duolite ES562	Novo Nordisk
Candida antarctica A	2.2	0.0	Powder	Fluka
Candida antarctica B	3.0	0.2	Powder	Fluka
Candida antarctica B (Novozym 435)	2.5	157.0	Immobilised on macroporous acrylic resin	Novo Nordisk (distributed by Fluka)

[a] Unit definition: one unit will hydrolyze 1.0 microequivalent of fatty acid from a triglyceride in 1 h at pH 7.7 at 37 °C.
[b] Reaction conditions: as given in the experimental section; ca. 23.2 mg enzyme; 45 °C.

Table 2
Characteristics of the Liqui-Cel® Hollow Fiber Module

Contactor type	Liqui-Cel® MiniModule 0.75 × 5
Shell diameter	19.05 mm
Overall contact area (based on outer fiber diameter)	0.12 m^2
Overall contact area (based on inner fiber diameter)	0.09 m^2
Number of fibers	1100
Outer fiber diameter	d_o = 300 μm
Inner fiber diameter	d_i = 220 μm
Fiber porosity	ε = 0.4
Pore tortuosity	τ = 2.25
Pore diameter	0.03 nm
Materials	
Membrane	Polypropylene
Shell	Polycarbonate
End piece	Polysulfone
Potting material	Epoxy

The distribution coefficients of the fluorous tagged compounds in two phase (fluorous-methanol) systems were determined by gravimetric method according to Barthel–Rosa and Gladysz [44]: ca. 0.5 g of the fluorous material was dissolved in 10 ml methanol, and then contacted in a separatory funnel with 10 ml of the fluorous solvent. The phases were allowed to separate, and the volatile liquids were removed under vacuum. The remaining fluourous compound in both phases was then determined by weighing. The mass balances closed to better than 1%, assuring that this gravimetric method gives reliable results.

The racemization of phenylethanol was investigated over various catalysts that had been proven to catalyze the Meerwein–Ponndorf–Verley (MPV) transfer hydrogenation of ketones to alcohols. We used a mesoporous SBA-15 onto which zirconium propoxide had been grafted, as well as an Al-free Zr–zeolite beta. For comparison, a normal zeolite beta was also investigated. These catalysts were prepared as described earlier [39,40].

3. Membrane-assisted separation

The membrane-assisted extraction used a system similar to that described by Baudot et al. [49]. The membrane contactor consists of a hollow fiber module containing a bundle of microporous polypropylene fibers. The unit is available from Celgard (Membrana) under the brand name Liqui-Cel® MiniModule®. Some properties of the unit are given in Table 2. The mini-module does not contain baffles in the shell-side, and flow is axial both in the shell- and lumen-side. The fluorous solvent (extraction solvent) is circulated through the lumen-side of the contactor, and the phase containing the material, which is to be extracted, is circulated through the shell-side. Under all experimental conditions, laminar flow prevails in the hollow fibers (Re < 50), so that mass transport from the center of the liquid to the membrane surface is largely confined to diffusive movement. It is therefore necessary to recycle both streams to achieve satisfactory approach to the distribution equilibrium. The solvents were circulated with peristaltic pumps (MasterFlex L/S with Easyload II pump head). A schematic of the extraction system is given in Fig. 1. Both streams were passed through the contactor in co-current mode so as to minimize the trans-membrane pressure (TMP) over the entire length of the contactor as we were plagued by pressure-driven leakage of one phase into the other. The set-

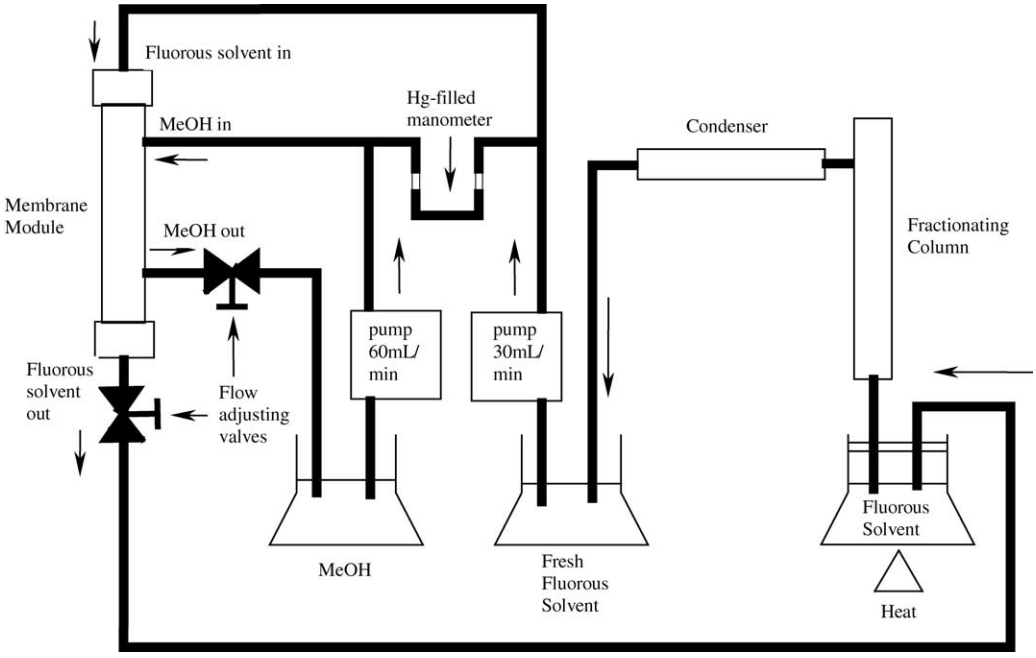


Fig. 1. Schematic of the apparatus for membrane-assisted extraction.

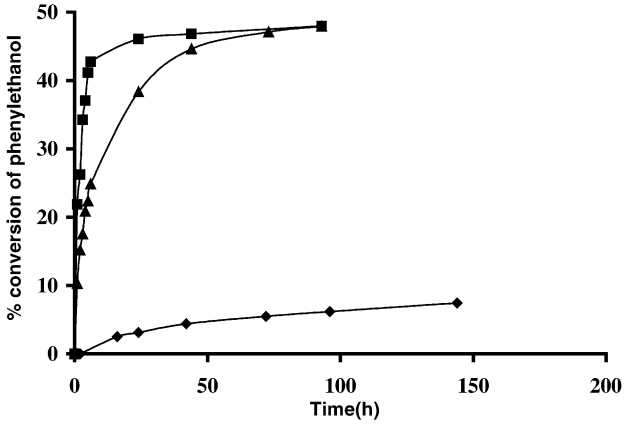


Fig. 2. Rate of transesterification of racemic 1-phenylethanol with different acyl donors mediated by Novozym 435 at 55 °C in TBME. (■) Isopropenyl acetate; (▲) fluorous ester 5; and (◆) ethyl trifluoroacetate.

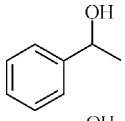
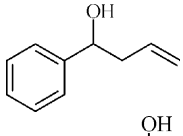
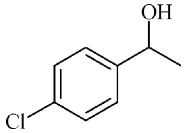
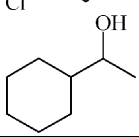
up incorporated a differential manometer to measure TMP, and pinch valves to adjust flow and pressure in the flow lines. The methanol, which was used as solvent, leads to considerable material compatibility problems. The original materials of the membrane module were not suitable: the plastic of the shell crazed and became brittle. It was necessary to machine a stainless steel housing for the hollow fiber membrane bundle. Likewise, the flexible tubing initially used (Tygon LFL) was not suitable: plasticizer leached out, and the tubes failed in the pump head. After extensive testing, we found that Pt-cured silicone tubing worked satisfactorily. Because of the low value of the distribution coefficient, a very large volume ratio of fluorous extraction solvent would be required. The high price of the fluorous solvents mandates to invent a scheme that allows one to conduct an efficient extraction with a small volume of solvent. We, therefore, pumped the extract into a rotary evaporator, where the solvent was evaporated. It was then re-condensed and fed back into the extractor. This set-up could be run at a flow of 30 ml/min for unlimited periods of time.

4. Results and discussion

Initially, several lipases from different sources were tested for the transesterification reaction in organic medium. As shown in Table 1, the activity for the transesterification in an organic medium does not at all correlate with the hydrolytic activity observed in an aqueous medium. However, it is apparent that lipase immobilized on a support performs much better than the unsupported enzyme. Notably, Novozym 435 (CALB immobilized on a macroporous acrylic resin) shows a very high activity. This enzyme preparation was therefore used in all subsequent experiments. The fluorous acyldonor **1** had an activity for the lipase catalyzed transesterification of secondary alcohols comparable to isopropenylacetate, the benchmark irreversible acyl transfer reagent (Fig. 2). Table 3 shows results for the successful fluorous tagging of a number of substrates.

Dynamic kinetic resolution requires the racemization of the undesired stereoisomer. We investigated the use of zeolites and mesoporous catalysts that had shown activity for the MPV reaction as racemization catalysts. In a MPVO reaction, the racemization comes about from the reversible reaction phenylethanol + acetophenone = acetophenone + phenylethanol. Acetophenone was therefore added to help in the intermediate oxidation of the 1-phenyl ethanol. Complete racemization of (*S*)-1-phenylethanol took place within 24 h over a 10 wt.% zirconium 1-propoxide grafted on a mesoporous silica support SBA-15 (40 mg catalyst; 0.40 mmol of (*S*)-1-phenylethanol and 0.40 mmol of acetophenone in 5 ml of TBME stirred at 55 °C) (Fig. 3).

Table 3
PFL-catalysed acylation of racemic secondary alcohols via fluorous phase labeling

Entry	Substrate	% Conversion	Time (h)	Rate[a] (μmol/h g enzyme)	% e.e.
1		50	49	50.9	98-(*R*)
2		21	173	6.1	99-(*R*)
3		45	198	11.4	99-(*R*)
4		45	107	21.0	>99-(*R*)

[a] Reaction conditions: as given in Section 2; ca. 23.2 mg enzyme; 45 °C.

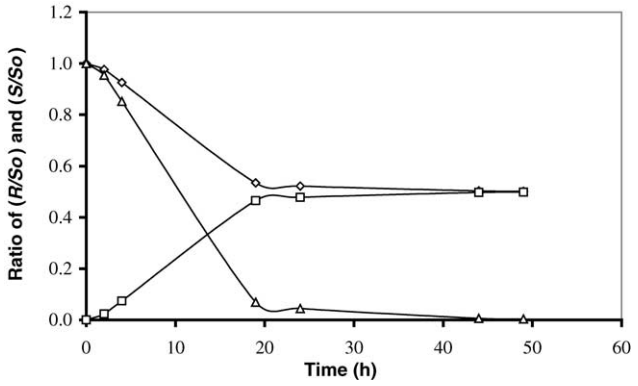


Fig. 3. Racemisation of (*S*)-1-phenylethanol. (□): R/S_o; (◇): S/S_o; (Δ): % e.e.; catalyst: zirconium propoxide grafted on mesoporous SBA-15; and 55 °C.

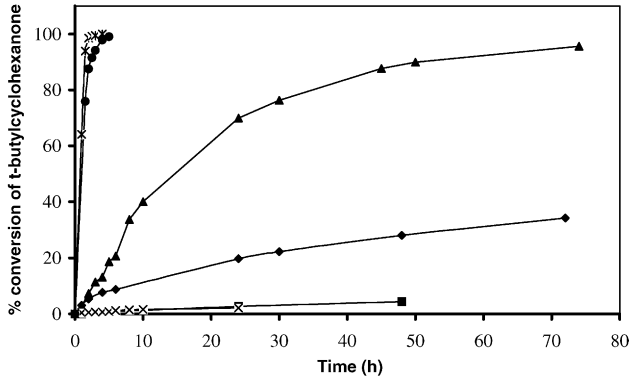


Fig. 4. Poisoning effect of isopropenyl acetate on various catalysts used in the MPV reduction of 4-*tert*-butylcyclohexanone. (*) Zr100 without ester; (●) Zr100 with ester; (▲) grafted SBA-15 without ester; (×) grafted SBA-15 with ester; (◆) beta zeolite without ester; and (■) beta zeolite with ester.

However, when we tried to combine the racemization with the kinetic resolution, we found that the acyl transfer reaction was somewhat accelerated, but proceeded again only to 50% conversion, where it stopped. For most of these measurements, isopropenyl acetate was used as acyl donor. We suspected that the acyl donor deactivated the catalyst. In order to investigate this further, we studied the influence of the acyl donor on the MPV reduction of 4-*tert*-butyl cyclohexanone (Scheme 2). The grafted SBA-15 catalyst was indeed completely deactivated by isopropenyl acetate at the test temperature of 55 °C. The low temperature was chosen to be compatible with the enzymatic reaction. Smaller pore Al-zeolite beta showed little activity for the MPV reduction under the test conditions. However, Al-free Zr-zeolite beta (Zr-100; Si/Zr = 100), which had been proven to be an excellent catalyst for the MPV reaction [40], showed a very high activity and was only slightly poisoned by the alkyl donor (Fig. 4).

Zr-100 was subsequently used for the dynamic kinetic resolution. From the poisoning experiments, it appeared that a higher temperature could prevent the adsorption of the ester at the active sites of the catalyst. Therefore, the heat stable lipase preparation Novozym 435 (lipase from *Candida antarctica*, isoform B) was used as biocatalyst. The reaction was conducted in toluene at 80 °C, without additional acetophenone. Fifty percent conversion was reached after 1 h. Thereafter, the reaction slowed down considerably, but it reached to 64% conversion after 24 h. The results are shown in Fig. 5. The enantiomeric excess decreased slightly with increasing conversion, and at 64% conversion, the e.e. was 89%. Adding equal amounts of phenylethanol and acetophenone accelerated the reaction, and 72% conversion was reached after 14 h and 90% conversion after 72 h. However, at equal conversion the e.e. was the same in both cases. These data are also shown in Fig. 5. In subsequent experiments, an enantiomeric excess of over 70% was realized at about 95% conversion. The reason for the decrease in stereo-selectivity could be one of the following: (1) the enzyme loses its selectivity at the higher temperature and also accepts the other isomer as substrate; (2) the MPV-catalyst also catalyzes a non-stereospecific transesterification or (3) the catalyst brings about the

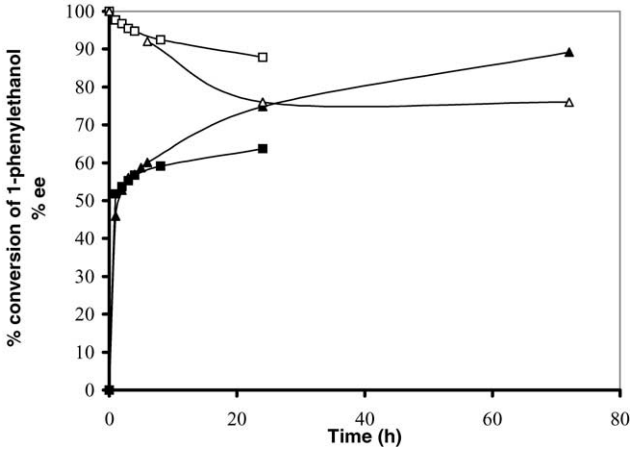
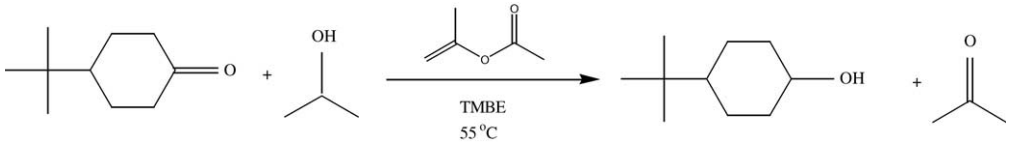


Fig. 5. Combination of enzymatic kinetic resolution and acid-mediated racemisation over Zr100. Open symbols: % e.e. (□) without acetophenone; (Δ) with acetophenone. Filled symbols: % conversion (■) without acetophenone; (▲) with acetophenone. Reaction conditions: 1.3 mmol 1-phenylethanol, 1.3 mmol acetophenone and 2.6 mmol isopropenyl acetate in 10 ml toluene; 100 mg Zr100 and 30 mg CAL-B. Reaction Temperature: 80 °C.



Scheme 2. MPV reduction of 4-*tert*-butylcyclohexanone in the presence of isopropenyl acetate.

racemization of the formed ester. Earlier experiments have shown that in the absence of the MPV catalyst, the enzyme retained its selectivity even at 80°C, and the conversion never increased above 50%. The enantiomeric excess remained constant at ~99% over several days of additional reaction. We found that the MPV catalyst can indeed promote the transesterification, but at a much slower rate (ca. 8% conversion in 17 h at 80 °C).

4.1. Membrane-assisted separation

The operation of the membrane-assisted fluorous extraction system requires some care in the initial adjustment of the flow-rates in order to minimize any pressure differential over the membrane. The low surface tension of the fluorous solvent allows it to easily move through the hydrophobic pores. However, after the adjustments were properly made, the separation progresses without further intervention. The system was tested with a mixture of rac 1-phenylethanol and fluorous tagged (*R*)-phenylethanol. After about 6 h continuous operation, when the extract had been exposed to 75 volumes of fluorous solvent, more than 90% of the fluorous ester was recovered from the evaporator. No phenylethanol passed into the fluorous phase.

5. Conclusion

The fluorous acyldonor **1**, which had been introduced by Theil and co-workers [45,49] can be used successfully for the lipase-catalyzed fluorous tagging of secondary alcohols. The immobilized lipase CAL-B, available under the trade name Novozym 435, shows a very high enantiomeric ratio, and the conversion rapidly reaches to the final value of 50%. At this point, both the faster reacting isomer (as the fluorous ester) and the unreacted (*S*)-1-phenylethanol are present is practically 100% enantiomeric purity. The solubility properties allow for the facile separation of the fluorous tagged (*R*-) isomer from the unreacted (*S*-) alcohol by extraction with a fluorous solvent. A scaleable process using a hollow fiber membrane contactor has been developed.

Dynamic kinetic resolution can be realized by coupling the enzymatic transesterification with the catalytic racemization of the secondary alcohol. Catalysts that are active for the MPVO reaction are also active for the racemization of secondary alcohols. However, the coupling with the biocatalytic transesterification is a problem because esters seem to tightly bind to the active site of many MPV catalysts. Zeolite Zr-beta was found to be a good racemization catalyst, which is also very tolerant to the presence of the acyl-transfer reagent. Conversion of up to 95% was achieved in the dynamic kinetic resolution of phenylethanol. However, the catalyst catalyzes some side reactions, and the enantiomeric excess at 95% conversion was only about 70%. Nevertheless, our study indicates that these zeolite-based catalysts can be used for racemization in a one-pot reaction. Work is under way to design bulkier acyl transfer reagents, which cannot enter the pore network of the zeolite racemization catalyst, and should therefore interfere less with the racemization reaction.

Acknowledgements

Support for this work by NUS (R-143-000-188-112 and R-143-000-201-112) is gratefully acknowledged.

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