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Dynamic Kinetic Resolution of a Wide Range of Secondary Alcohols: Cooperation of Dicarbonylchlorido(pentabenzylcyclopentadienyl)ruthenium and CAL-B

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The substrate scope in the dynamic kinetic resolution of secondary alcohols was studied by using 31 structurally different alcohols and isopropenyl acetate in the presence of dicarbonylchlorido(pentabenzylcyclopentadienyl)ruthenium and *Candida antarctica* lipase B (Novozym 435, CAL-B) in toluene. The enzyme and the ruthenium complex were shown to function in a highly compatible manner allowing the conversion of the racemic alcohols into the (*R*)-acetates in practically theoretical yields and, in most cases, *ee* values exceeding 99%. The results are fully comparable to those published previously by using earlier reported, state-of-the-art ruthenium-based catalysts for the alcohol racemization. A clear benefit of the dicarbonylchlorido(pentabenzylcyclopentadienyl)ruthenium system, when compared to other (cyclopentadienyl)ruthenium racemization catalysts, is its simple and cost-efficient preparation.

Introduction

Lipases (EC 3.1.1.3) are most commonly used as enantioselective biocatalysts in the kinetic (KR) and dynamic kinetic (DKR) resolutions of racemic alcohols.[1] This is a natural consequence of their good availability and excellent regio- and stereoselectivity in addition to their stability in a variety of reaction media, including organic solvents and ionic liquids, which dissolve organic substrates better than aqueous environments do. Lipases also accept a broad range of structurally different alcohols (or more generally nucleophiles) and carboxylic acids and their derivatives as substrates in addition to the natural substrates, triglycerides. The KR method, affording in the best case both enantiomers of a racemic mixture at 50% conversion in a single reaction, is beneficial when both enantiomers are important. In such a case, one enantiomer remains unchanged, while the other becomes the new reaction product. Especially lipase-catalyzed enantioselective acylation of racemic secondary alcohols with achiral esters in organic solvents has afforded a large number of alcohol enantiomers to be used as such or as intermediates for further transformations into pharmaceutically active compounds and fine chemicals. On the other hand, the concept of lipase-catalyzed DKR combines the enzyme with a chemical or enzymatic racemization catalyst, allowing continuous racemization of the unreacted alcohol enantiomer and accordingly the transformation of the racemic mixture into the product ester in 100% theoretical yield, not reachable in the corresponding kinetic resolution. The absolute configuration of the acylated product then depends on the enantiopreference of the enzyme, the fact which may limit the use of DKR in cases where a lipase [usually (*R*)-selective when the large group at the asymmetric center has priority over the medium-size group like with (*R*)-1-phenylethanol] produces the product as the undesired enantiomer. In some cases, Subtilisin Carlsberg (a serine protease) with opposite enantiopreference to that of most lipases has been used in overcoming the problem.[2]

Candida antarctica lipase B (CAL-B as a Novozym 435 preparation) and suitable transition-metal catalysts form combinations extensively studied in the DKR of racemic alcohols.[3] The concept was first introduced by Williams[4] and Bäckvall[5] in the late 1990s. Thereafter, various metal catalysts have been shown to racemize alcohols. However, only certain metal catalysts maintain the crucial requirements of full racemization power together with stability during DKR. Half-sandwich ruthenium complexes **1**–**3** represent this far the most successful and applied racemization catalyst design for the DKR of various types of secondary alcohols with CAL-B (Figure 1). The initially employed Shvo catalyst **1** requires elevated temperatures for generating the active monoruthenium species,[3] whereas the monomeric ruthenium complexes **2**[6] and **3**[7] can be utilized at ambient temperatures by activation with potassium *tert*-butoxide. Nevertheless, the ruthenium-based complexes **1**–**3**

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can be considered far from optimal, especially in terms of cost and ease of preparation. With this in mind, we have earlier reported the simple and cost-efficient preparation of dicarbonylchlorido(pentabenzylcyclopentadienyl)ruthenium (**4**) bearing benzyl substituents on the cyclopentadienyl ring instead of the phenyl groups of **1**–**3**.[8] A clear benefit in the synthesis of complex **4** is the simple preparation of its ligand precursor by alkylation of cyclopentadiene with benzyl alcohol facilitated by azeotropic water removal under basic conditions.[9] An additional advantage of complex **4** is its considerably higher solubility induced by the benzyl substituents when compared with the polyphenylcyclopentadienyl-ligated catalysts, which – in some cases, in solvents commonly used for DKR reactions – may operate at the limits of solubility. In previous work we have shown that complex **4** forms an active racemization catalyst for the DKR of 1-phenylethanol and 1-(furan-2-yl)ethanol with CAL-B in toluene, providing effectiveness in terms of yield and enantiopurity comparable to the best ruthenium catalyst **3** reported in the literature.[8a] It was also previously demonstrated that both **3** and **4** are applicable in a large-scale DKR, transforming racemic 1-phenylethanol [at a 1 mol (122 g) scale] into the (*R*)-acetate with excellent yield and *ee* > 99%.[8b,10]

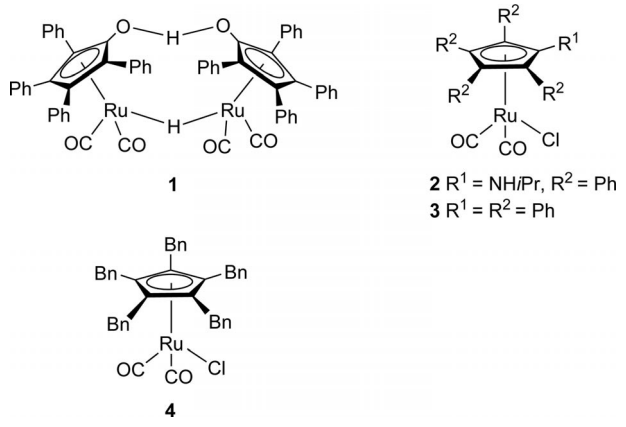
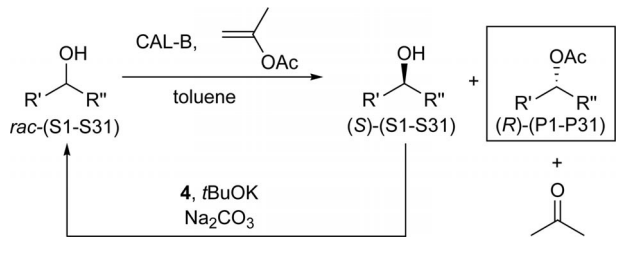


Figure 1. Half-sandwich ruthenium complexes **1**–**4**.

Our aim herein has been to study further the general usability of complex **4** as a racemization catalyst in the DKR of secondary alcohols. For this purpose, 31 alcohols (structures S1–S31, in accordance with the entries in Table 1) were subjected to acylation with isopropenyl acetate in the presence of CAL-B and ruthenium catalyst **4** in toluene (Scheme 1). The reactions were performed in a glovebox under nitrogen.



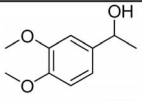
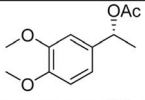
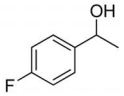
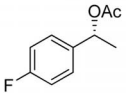
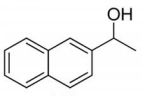
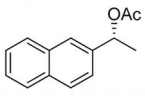
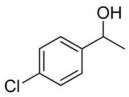
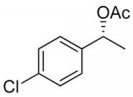
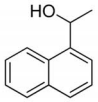
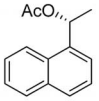
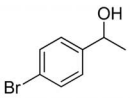
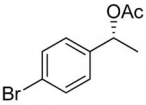
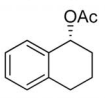
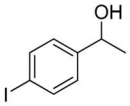
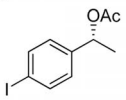
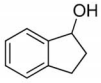
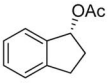
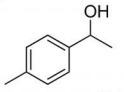
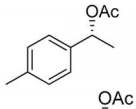
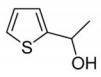
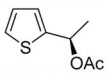
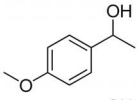
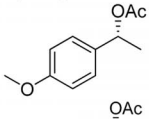
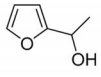
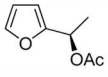
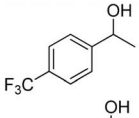
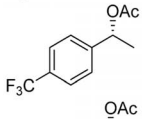
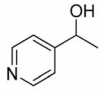
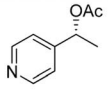
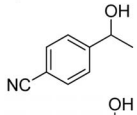
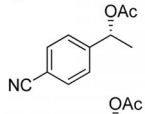
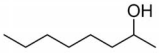
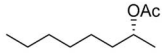
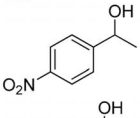
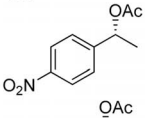
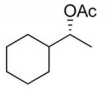
Scheme 1. DKR of secondary alcohols with **4**; alcohols involved shown in Table 1.

Results and Discussion

The scope and limitations of the dynamic kinetic resolution method utilizing complex **4** and CAL-B (Novozym 435) were studied by subjecting a wide range of structurally varying secondary alcohols (substrates S1–S31) to acylation with isopropenyl acetate in toluene at room temperature (23 °C) in a glovebox under nitrogen with water and oxygen contents below 1 ppm (Scheme 1). Due to the low racemization rate of substrate S24 its DKR was performed at 60 °C in a tightly closed glass bomb. The bomb was charged in the glovebox and heated in an oil bath in a fume hood. Toluene was chosen as a solvent as it had already been proved to be well accepted by both the lipase and the ruthenium complex **4**.[8] Toluene also dissolves the aromatic secondary alcohols and ester products relatively well and is accepted for industrial applications. One of the benefits of enzymatic synthesis is that enzymes allow effective reactions at ambient temperatures, reducing the formation of possible side products. Such a side product, the formation of which was avoided herein, is the formation of the ketones from the corresponding alcohol substrates. To ensure reproducibility and reliability of the system, parallel reactions were performed. The (*R*)-ester products were isolated for each substrate by column chromatography in excellent (90–99%) yields as shown in Table 1. The alcohols S1, S3, S7–S10), S18, S19, S22–S28 and S30 were selected due to their previously reported promising behavior in the DKRs employing (pentaphenylcyclopentadienyl)ruthenium complex **3** and CAL-B. The DKR results reported for these substrates earlier are shown in Table 1 in *italics*.[7c] The remaining 14 secondary alcohols were selected for extending the structural diversity and due to their importance as enantiopure compounds for different purposes in synthetic chemistry. To exemplify, alcohols S7, S13 and S16 are versatile building blocks for cross-coupling reactions.[11] The DKRs of polyfunctional substrates bearing conventional and easy to remove protective groups in turn, such as methoxymethyl ether (MOM) and *tert*-butoxycarbonyl (Boc) in S11 and S12, have not been described before. Also the DKRs of *ortho*-substituted alcohols S14–S16 and that of S17 have not been disclosed earlier. The reactions reaching full conversion (no remaining substrate alcohol detected by chiral GC analysis) are indicated with yields > 99%. Possible formation of the corresponding ketone (a side product) from the alcohol in question was also carefully monitored by GC. In most cases ketones were not detected, and when observed (substrates S7, S20, S21, and S25), the levels were negligible (≤ 1%).

Compatibility of the chemo- and the enzymatic biocatalysts in DKR indicates that the enzymatic KR of the racemic alcohol remains enantioselective and that the racemization of the less reactive alcohol enantiomer is fast compared

Table 1. Dynamic kinetic resolution of secondary alcohols (1 mmol) with isopropenyl acetate (1.2 mmol) catalyzed by **4** (2 mol-%) and CAL-B (10 mg) in the presence *t*BuOK (2.5 mol-%) and Na_2CO_3 (0.5 mmol) under nitrogen in toluene (2 mL) at 23 °C. Data in *italics* from ref.[7c]: substrate (1 mmol), **3** (5 mol-%), CAL-B (6 mg), *t*BuOK (5–8 mol-%), Na_2CO_3 (1 mmol) in toluene (2 mL). Conversions and *ee* values are averages of at least 3 reaction runs.

Entry	Substrate S1–S31	Time [h]	Product P1–P31	Yield[a,b] [%]	*ee*[a] [%]	Entry	Substrate S1–S31	Time [h]	Product P1–P31	Yield[a,b] [%]	*ee*[a] [%]
1		3 *3*		>99 (95) *95 (92)*	>99 *>99*	17		18		>99 (98)	>99
2		3		>99 (99)	>99	18[f]		6 *3*		99 (96) *93*	>99 *>99*
3		3 *3*		>99 (93) *93 (91)*	>99 *>99*	19[f]		120 *24*		>99 (94) *>97 (97)*	99[e] *>99*
4		3		>99 (94)	>99	20		36		97 (96)	>99
5		3		>99 (96)	>99	21		24		95 (92)	98
6		3		>99 (97)	>99	22		24 *6*		99 (90) *98 (98)*	>99 *>99*
7		3 *3*		>99 (99) *96 (94)*	>99 *>99*	23		9 *6*		98 (94) *93*	>99 *96*
8		6 *24*		>99 (95) *>98 (98)*	>99 *>99*	24[g,h]		24 *20*		>99 (90) *97 (96)*	>99 *99*
9		30 *20*		99 (92) *98 (95)*	>99 *>99*	25		3 *20*		>99 (99) *93*	97 *>98*
10		96 *20*		98 (95) *99 (97)*	98 *>99*	26		3 *17*		98 (94) *98*	>99 *>99*
11		3		99 (95)	>99	27		9 *17*		>99 (99) *92 (90)*	>99 *>99*
12[c]		24		>95[d] (98)	98[e]	28		6 *6*		>99 (96) *99*	93 *91*
13		6		>99 (95)	>99	29		3		>99 (96)	94
14		24		>99 (93)	96	30		3 *18*		>99 (99) *89*	98 *>99*
15		9		>99 (97)	>99	31[i]		168		99 (96)	95
16		168		>99 (91)	>99						

[a] Unless otherwise noted, determined by chiral GC. [b] Isolated yield in parentheses. [c] Toluene/THF mixture (4:1, 5 mL). [d] Determined by NMR spectroscopy. [e] Determined by NMR spectroscopy as the corresponding Mosher's ester. [f] Toluene used 4 mL. [g] Toluene/THF mixture (4:1, 2.5 mL). [h] 60 °C. [i] CAL-B (40 mg).

to the enzymatic acylation. Moreover, other reagents such as added bases used to activate the chemocatalyst should not influence the enzyme nor should they result in chemocatalytic ester formation/decomposition. Products of enzymatic reactions, such as acetone, should not destroy the chemocatalyst. Under the conditions of such compatibility, the less reactive alcohol can be expected to remain racemic throughout the DKR, allowing the estimation of the theoretical enantiomeric excess (*ee*) attainable for the ester product in DKR by extrapolating the plot of product *ee* vs. conversion in the corresponding KR to zero conversion as enables the use of the Sih and Chen equation and the *E* value.[12] It is often concluded that $E = 20$ is a limit for successful KR. It may be worth to emphasize that the KR then can produce only the unreacted enantiomer enantiopure at over 60% conversions, while the theoretical maximum product *ee* (and the theoretical *ee* in DKR) is only 90%. For the DKR to lead to product formation with *ee* = 99%, $E = 200$ or higher is necessary in the corresponding KR.

In the DKR of the alcohols S1–S31 with isopropenyl acetate catalyzed by complex **4** and CAL-B in dry toluene, possible side reactions (other than ketone formation from the alcohol) are the hydrolysis of isopropenyl acetate/(*R*)-ester produced by enzymatic action and the formation of racemic esters P1–P31 caused by the presence of *t*BuOK. Water (often called residual water) for ester hydrolysis originates from the seemingly dry enzyme preparation. This is particularly possible with CAL-B as the Novozym 435 preparation (CAL-B adsorbed on a divinylbenzene-crosslinked, hydrophobic macroporous polymer based on methyl and butyl methacrylic esters), because this lipophilic immobilization material will readily release any water into the dry reaction mixture.[13] Moreover, a water tunnel, existing in some enzymes and allowing an easy access for water directly from the medium to the active site, was previously found in CAL-B.[14] Accordingly, the residual water as a nucleophile can easily hydrolyze the acyl-enzyme intermediate [formed in the first mechanistic step of a reaction catalyzed by serine hydrolases when an achiral acyl donor/the (*R*)-ester or -acid produced reacts with the serine hydroxy group] at the active site in an otherwise dry system. As a consequence, some acetic acid from isopropenyl acetate is formed when the DKR proceeds. An active intermediate formed from the ruthenium catalyst **4** when activated with *t*BuOK is unstable in the presence of acids. One reason for the good compatibility of CAL-B and complex **4** (as well as complexes **1**–**3**)[3,7] observed in toluene is certainly the hydrophobic nature of the solvent minimizing the ability to stipe the residual water from the immobilized CAL-B. Thus, Na_2CO_3 must be added to neutralize the formed acetic acid in situ. The strongly basic *t*BuOK in equivalent amounts to complex **4** is used for the activation. Care is needed to retain the content of *t*BuOK as low as possible in order to prevent nonenzymatic chemical formation of racemic esters, lowering the product *ee*. If not carefully controlled, chemical ester formation can be considerable, especially in the beginning of the DKR. With this in mind, we focused on optimizing the reaction system especially with respect to the catalyst loadings. After thorough drying of all the components and transferring of the mixture under nitrogen into a glovebox, we were able to decrease the Ru-catalyst loading by one half (from 4 mol-% to 2 mol-%) in a 1 mmol scale reaction without loosing in efficiency of the system. Earlier the decrease in the catalyst loading from 4 mol-% has required a significant increase in reaction scale to ensure efficient racemization.[10] Reduction in the amount of isopropenyl acetate to 1.2 equiv. over the substrate alcohol (1.5 equiv. was previously used[8b]) affected the acetic acid content of the mixture, allowing the amount of Na_2CO_3 to be reduced to half of what was used before. Under such conditions the (*R*)-esters were obtained in excellent enantiopurities [*ee* mostly $> 99\%$, i.e., only one enantiomer was observed by chiral GC analysis (Table 1)]. This is in accordance with the excellent enantiopurities observed earlier by Bäckvall and co-workers under their DKR conditions for secondar alcohols (Table 1).[7c]

The time required for reaching full conversion in DKR is one measure of its effectiveness. The comparison of literature results that are based on the use of lipase catalysis in KR and DKR is not always straightforward (although often performed in the literature), as the activity of the enzyme is rarely given and may differ from case to case. Comparison of the DKR results of our work with catalyst **4** and the published work[7c] with catalyst **3** is not an exception in this respect. For the results in Table 1, the amount of CAL-B was set to 10 mg to match such reactivity that the DKR of 1-phenylethanol (1 mmol) reached full conversion in 3 h as given in the published method by utilizing complex **3**[7c] (Entry 1). Based on initial rate measurements for the acylation of racemic 1-phenylethanol (0.5 M) with isopropenyl acetate (0.6 M) in toluene, enzymatic activity of $2.6\ \text{mmol}\,\text{min}^{-1}\,\text{g}^{-1}$ was obtained for the CAL-B preparation used throughout the present work. In spite of the above-mentioned discrepancy, clear reactivity differences can be proposed for DKRs with complexes **3** and **4** with alcohols S8, S10, S25–S27 and S30. Differences in reactivity are observed both ways, alcohols S8, S26, S27 and S30 being more reactive in the presence of complex **4**, whereas the opposite is observed for alcohols S10, S19 and S22. This may reflect some mechanistic differences between the two racemization catalysts but may also be due to the presence of minor impurities acting as enzyme inhibitors or poisons for the racemization catalyst.

The results in Table 1 show that in the DKRs using CAL-B with either complex **3** or **4**, the nature of the *para* substituents (electron-donating/electron-withdrawing) in 1-phenylethanols has not a clear effect on the reactivity (S2–S7, S11 and S12 vs. S1), the most electronegative substituents *p*-CF_3, *p*-CN and *p*-NO_2 in S8–S10 being exceptions. As is shown for products P4 and P5 in the Supporting Information, dehalogenated P1 was seen in the GC chromatograms. As the dehalogenated products (3 mass-% with S4 and 1.5 mass-% with S5) were detected also in the ^{1}H NMR spectra of isolated products it is possible that the product is formed in the DKR process. In the DKR of 1-(4-ni-

trophenyl)ethanol (S10), the observations suggest the decay of the ruthenium catalyst **4** but not that of the catalyst **3**. When the DKR was performed with catalyst **3** under otherwise similar conditions, conversion over 95% was reached in only 8 h, whereas the same conversion took 4 d in the presence of complex **4** (conversions monitored by ^{1}H NMR spectroscopy). Moreover, the color of the activated complex **4** changed immediately to an intensive dark cherry color when S10 was added; *ortho* and *meta* substitutions both increased the time required to complete the DKR (S13–S17 vs. S1). With *ortho*-substituted 1-phenylethanols considerable retardations in the reactivity were observed with S14–S16 possibly due to steric effects, the effect of the *o*-Br substituent in the DKR of S16 being more than expected (7 d to full conversion). The transformation of bulky bicyclic secondary alcohols S18–S21 into the corresponding (*R*)-acetates in quantitative yields was also possible in the presence of complex **4**. The DKR of 1-naphthylethanols, that of 1-(1-naphthyl)ethanol in particular (Entry 19), is interesting since again the presence of **4** leads to a low reactivity compared to the reported result with **3**.[7c] Also, different heterocyclic secondary alcohols S22–S24 were converted into the corresponding highly enantiopure acetates within reasonable reaction times. In the case of 1-(4-pyridyl)ethanol (S24) elevated reaction temperature (60 °C) was needed to accomplish the DKR. 2-Octanol (S25) and 1-cyclohexylethanol (S26) were also smoothly transformed into the corresponding (*R*)-acetates in high yields. The DKR of aromatic secondary alcohols S27–S29 with the alcoholic hydroxy function at different positions of the carbon chain gave fast reactions and excellent yields. The DKRs of S30 and S31 produced the (*R*)-acetates in high yield and enantiopurity without side reactions with our complex **4**. Significant ketone formation was previously reported for the DKR of S30 in the presence of catalyst **3**.[7c] Ketone formation was not a problem in our studies with complex **4**.

Conclusions

After thorough optimization, the dicarbonylchlorido-(pentabenzylcyclopentadienyl)ruthenium (**4**) and CAL-B catalyzed DKR of a wide range of structurally varying secondary alcohols was studied by using the acylation with isopropenyl acetate in toluene. The use of a glovebox allowed convenient and controlled conditions for reliable and reproducible reactions and convenient sample taking. The secondary alcohols studied were transformed into highly enantiopure (*R*)-acetates (mostly *ee* > 99) in close to quantitative yields, the reaction times needed for full conversions considerably depending on the substrate structure. Since the ruthenium complex **4** catalyzed the in-situ racemization of the less reactive alcohol enantiomers effectively, the lipase-catalyzed resolution reaction became rate-limiting in the overall reaction. The DKR results in the presence of racemization catalysts **3** and **4** are comparable in most cases. However, clear differences in the reactivity can be seen with alcohols S8, S10, S25–S27 and S30. In the DKR of 1-(4-nitrophenyl)ethanol (S10), the observation suggests the decay of the ruthenium catalyst **4**.

The simple, cost-effective and high-yield preparation of **4** together with its high performance makes this complex an attractive candidate as leading racemization catalyst for future DKR applications.

Experimental Section

Dynamic Kinetic Resolution: Ruthenium complex **4** (14 mg, 20 μmol), CAL-B (10 mg) and Na_2CO_3 (53 mg, 0.5 mmol) were weighed into a pre-dried test tube in a glovebox, and toluene (1 mL) was added. The mixture was stirred for 2 min before a solution of *t*BuOK (0.25 M in THF; 100 μL, 0.025 mol) was added. After stirring for 5 min, one of the substrates S1–S31 (1 mmol) was introduced, and the mixture was stirred for another 5 min before the addition of isopropenyl acetate (135 μL, 1.2 mmol). The reactions were monitored by taking samples (10 μL), derivatizing them with propionic anhydride in the presence of DMAP in pyridine (1%), filtering the samples through silica by using ethyl acetate as an eluent in order to prevent contamination of the gas chromatograph with ruthenium and analyzing them by GC. Isolation of the products was performed by silica gel column chromatography eluting with hexane/CH_2Cl_2 (nonvolatile products), with pentane/CH_2Cl_2 (volatile products) or with hexane/AcOEt [(*R*)-1-(4-pyridyl)ethyl acetate]. NMR spectroscopic data and optical rotation values for isolated products can be found in the Supporting Information.

Initial Rate Measurements and Enzyme Activity: 1-Phenylethanol (120 μL, 1 mmol) was added to a reaction vessel containing CAL-B (3 mg) and toluene (2 mL). The acylation was initialized by adding isopropenyl acetate (135 μL, 1.2 mmol). The reactions were monitored by taking samples at intervals, filtering off the enzyme and analyzing the samples by GC equipped with a chiral column after derivatization with propionic anhydride in the presence of DMAP in pyridine (1%).

Determination of the Enantiomeric Excess by NMR Spectroscopy: Isolated acetates were first subjected to alkaline hydrolysis,[15] and the obtained alcohols were then converted into the corresponding (+)-(*S*)-MTPA esters[16] according to standard procedures. Dichloromethane was used as a solvent instead of tetrachloromethane due to the toxicity of the latter. Determination of the *ee* values was performed by comparing integral intensity of the minor and the major diastereomers.

Supporting Information (see footnote on the first page of this article): Experimental Section, GC and spectral analyses of the prepared (*R*)-acetate esters of secondary alcohols P1–P31 obtained in the DKR of S1–S31.

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