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Efficient dynamic kinetic resolution of secondary alcohols with a novel tetrafluorosuccinato ruthenium complex

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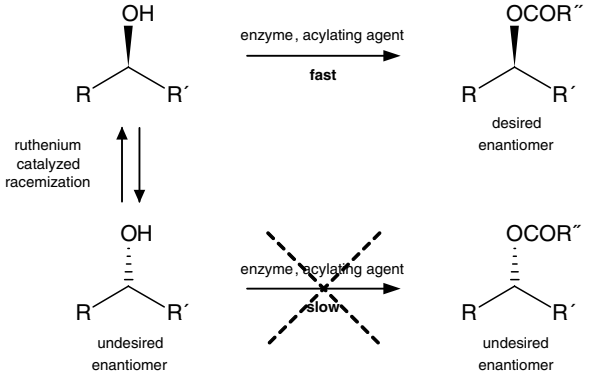
Abstract—Dynamic kinetic resolution (DKR) of a series of secondary alcohols has been conducted with a novel dinuclear ruthenium complex, bearing tetrafluorosuccinate and (*rac*)-BINAP ligands as the racemization catalyst. Novozym 435 has been used as the enzyme, and isopropyl butyrate as the acyl donor. Five substrates underwent DKR successfully: an aliphatic and an aromatic secondary alcohol, an aromatic alcohol with an electron-withdrawing substituent on the phenyl ring, an aromatic alcohol bearing an electron-donating substituent on the ring and a heteroaromatic secondary alcohol. The catalyst performed optimally at 70 °C. Typically the reaction reached complete conversion within 1 day with 0.1 mol % of racemization catalyst relative to the substrate. The addition of the ketone corresponding to the substrate stabilizes the active Ru complex and, therefore, increases the rate of the reaction.

1. Introduction

Over the past decade, there has been an ever increasing demand for enantiopure compounds, mainly for pharmaceutical applications. Different enantiomers, in general, exhibit different biological activities and easy access to these compounds is, therefore, of paramount importance. Optically active secondary alcohols are valuable building blocks for such pharmaceuticals. These alcohols can be produced by asymmetric synthesis from the corresponding ketone, which is usually readily available using either enzymatic or chemo catalysis.[1,2] However, on an industrial scale, enantiopure alcohols are often isolated by resolution of the corresponding racemate.[3] Many approaches are based on the (*R*)-selective lipase catalyzed transesterification of secondary alcohols, which normally proceed with high enantioselectivity. An inherent drawback of this strategy is that the maximum yield is limited to 50%.

A solution for this problem is presented by chemoenzymatic dynamic kinetic resolution (DKR). In this application of tandem catalysis, in situ racemization enables the complete conversion of the racemate into the desired enantiomer (Scheme 1).[4] In principle, 100% of the (*R*)-ester can hence be obtained with 100% ee from a racemic alcohol. Many substrates were converted into the enantiopure ester with good yields, including a broad range of substituted aromatic and aliphatic secondary alcohols and secondary diols. The (*S*)-esters could be obtained when using subtilisin instead of a lipase and with the appropriate ruthenium catalyst, even chiral primary amines were selectively



Scheme 1. Dynamic kinetic resolution of secondary alcohols.

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transformed into the corresponding (*R*)-amide via DKR.[5] In a similar approach, we and others have recently reported on the conversion of a racemic monomer into the enantiopure polymer.[6] (*R*)-Polyesters were obtained in good yield and selectivity from ω-substituted ε-caprolactones.

In the literature, the performance of various Ru-based racemization catalysts has been reported. The performance of these Ru catalysts varied considerably. Bäckvall et al. recently reported that the racemization catalyst [(Ph_5Cp)-$Ru(CO)_2X$] (X = Cl, Br) enables DKR at ambient temperature with reaction times ranging from 3–24 h for most substrates, although it required 5 mol % of Ru catalyst.[4e,f]

Early investigations used *p*-chlorophenyl acetate as the acyl donor, since *p*-chlorophenol does not interfere with the racemization reaction.[4b] However, due to environmental and economic considerations, this acyl donor is highly undesirable. Verzijl et al. developed a process to perform the DKR using simple esters, such as isopropyl butyrate.[4g,7] The isopropanol formed by the transesterification is continuously removed at reduced pressure. This approach enables a large scale application of DKR.

Recently, we introduced a novel dinuclear ruthenium complex bearing tetrafluorosuccinate and phosphine ligands (Fig. 1).[8] Promising results were obtained in the acceptorless dehydrogenation of 1-phenylethanol. We then became interested in its application as a racemization catalyst in DKR. Herein, we report on the DKR of various secondary alcohols using complex **1** as the racemization catalyst giving high yields and high ee.

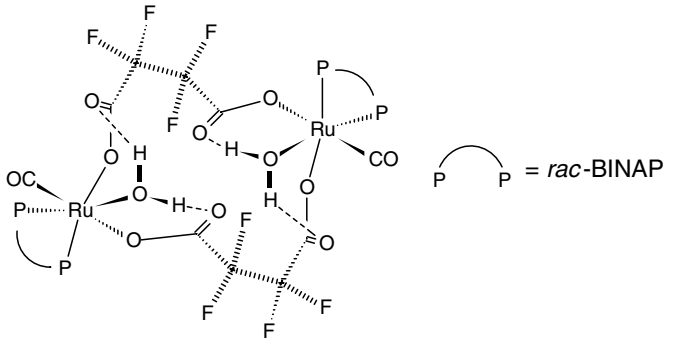

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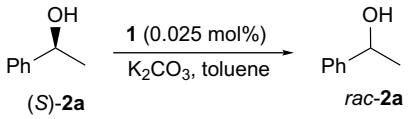
Figure 1. Dinuclear ruthenium complex bearing tetrafluorosuccinate and phosphine ligands (complex **1**).

2. Results and discussion

2.1. Racemization of (*S*)-1-phenylethanol

First the racemization of (*S*)-1-phenylethanol (*S*)-**2a** was investigated. The reaction was carried out with complex **1** as the racemization catalyst and with toluene as the solvent. K_2CO_3 was used to activate the catalyst (Scheme 2).

In order to determine the optimal reaction conditions, the racemization of (*S*)-**2a** was performed at 70 °C and 100 °C

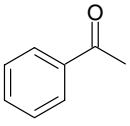
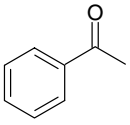
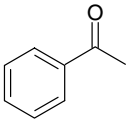
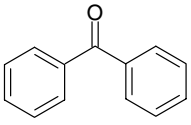
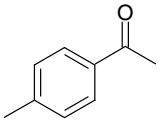
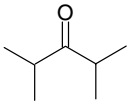


Scheme 2. Racemization of (*S*)-1-phenylethanol.

with and without the presence of acetophenone **3a**. Presumably, the active catalyst deactivates in the absence of acetophenone (Table 1, entries 1 and 2); the best result was obtained at 70 °C. When the conversion is defined according to Eq. 1, it can be derived that the racemization obeys first-order kinetics[9]

$$X(t) = 1 - \frac{\mathrm{ee}(t)}{\mathrm{ee}(0)} \tag{1}$$

Table 1. Racemization of **2a** using **1** as a racemization catalyst[a]

Entry	*T* (°C)	Ketone (mmol)	Time (min)	ee[b] (%)
1	70	No ketone	180	6.5
2	100	No ketone	180	27.1
3	70	 **3a** (0.7 mmol)	180	0.5
4	100	 **3a** (0.7 mmol)	40	0.1
5	100	 **3a** (1.0 mmol)	80	0.4
6	100	 **4a** (1.1 mmol)	80	1.0
7	100	 **4b** (0.9 mmol)	40	0.2
8	100	 **4c** (1.0 mmol)	180	3.3

[a] Reaction conditions: (*S*)-**2a** (4.5 mmol), toluene (4.5 mL), ketone **3a** or **4a–c**, catalyst **1** (0.0011 mmol) and K_2CO_3 (1.5 mmol), Ar atmosphere.
[b] Determined by chiral GC; calculated values.

A linear relationship between $-\ln(1 - X)$ and time (t) can then be obtained. Figure 2 shows a short induction period during the first minutes of the reaction, which is attributed to activation of the catalyst by K_2CO_3. In the absence of **3a**, first-order kinetics is not obeyed (Fig. 2, entries A and B) and a dramatic reduction of the rate of racemization is observed. Moreover, catalyst deactivation is faster at 100 °C.

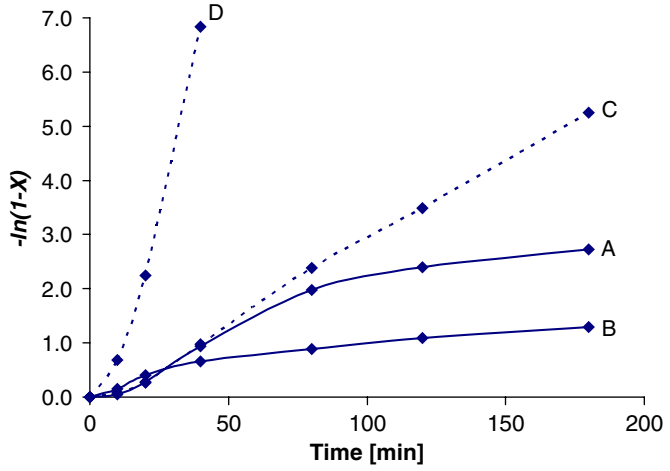
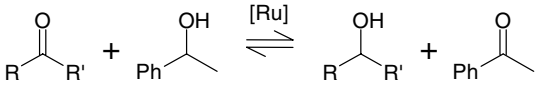


Figure 2. $-\ln(1 - X)$ as a function of time for the racemization of (*S*)-**2a** catalyzed by complex 1 (0.025 mol %) without acetophenone at 70 °C (A; Table 1, entry 1) and at 100 °C (B; Table 1, entry 2) and in the presence of acetophenone at 70 °C (C; Table 1, entry 3) and at 100 °C (D; Table 1, entry 4).

The addition of **3a** to the reaction mixture resulted in first-order behavior at 70 °C as well as at 100 °C. It should be noted that at 100 °C, the presence of acetophenone resulted in a dramatic increase in the rate of racemization (Table 1, entries 4 and 5; Fig. 2, entry D). Apparently, the presence of **3a** keeps the catalyst active. An optimal rate of reaction was obtained when 0.7 mmol of **3a** was added (16 mol % in relation to the substrate) (Table 1, entry 4); larger amounts reduced the rate of racemization, probably because of occupation of the active site of the catalyst by **3a**.

To gain more insight into the reaction mechanism, the influence of other ketones on the racemization of (*S*)-**2a** was also investigated (Table 1, entries 6–8).[10] Apparently, all ketones stabilized the active catalyst, as first-order kinetics was obeyed in all cases.

The results of the racemization reactions in the presence of ketones, benzophenone **4a** or 4-methyl-acetophenone **4b**, demonstrated that the catalyst activity was similar to that with acetophenone **3a** (Table 1, entries 6 and 7). Transfer hydrogenation was observed, resulting in the rapid formation of the corresponding alcohol as well as acetophenone (Scheme 3). At equilibrium, 80–100% of the original ketone



Scheme 3. Transfer hydrogenation of ketones and 1-phenylethanol.

was converted to acetophenone. The equilibrium, as given in Scheme 3, was reached before racemization was complete, indicating that the racemization occurs via transfer hydrogenation. This contrasts with the racemization mechanism, which was reported for $[(Ph_5Cp)Ru(CO)_2Cl]$.[4f] For $[(Ph_5Cp)Ru(CO)_2Cl]$, it was determined that the ketone obtained from the alcohol remains in the coordination sphere of the Ru atom during racemization and does not exchange with the free ketone. With aliphatic diisopropyl ketone **4c**, transfer hydrogenation was considerably slower, resulting in a concomitantly lower rate of reaction (Table 1, entry 8).

2.2. DKR of secondary alcohols

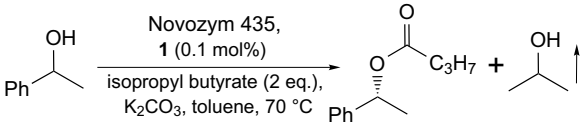
DKR of **2a** was carried out with immobilized *Candida antarctica* Lipase B (Novozym 435) as the enantioselective acylating catalyst and ruthenium catalyst **1** as the racemization catalyst. Isopropyl butyrate was used as the acylating agent and isopropanol was removed at a reduced pressure.[7] DKR of **2a** was performed with and without the presence of **3a**, using only 0.1 mol % of complex **1** with respect to the substrate. DKR without a ketone is preferred, since the isolation of the product is less complicated.

High yields and excellent ee values were obtained for each entry (Table 2). Figure 3a shows the conversion based on enantiomeric balance (eb) versus time. The eb is a measure of the conversion of the (*S*)- into the (*R*)-enantiomer (see Eq. 2)[7]

$$X_{\mathrm{eb}}(t) = \frac{N_{R\text{-alcohol}}(t) + N_{R\text{-ester}}(t) - N_{S\text{-alcohol}}(t) - N_{S\text{-ester}}(t)}{N_{R\text{-alcohol}}(t) + N_{R\text{-ester}}(t) + N_{S\text{-product}}(t) + N_{S\text{-ester}}(t)} \quad (2)$$

In Figure 3b, the ee of **2a** during the reaction is depicted. Enzymatic transesterification results in a rapid increase of the ee of **2a** during the first hours of the reaction [conversion of (*R*)-**2a** into (*R*)-**5a**]. At higher conversions, the amount of racemization catalyst **1** in the reaction mixture in relation to the substrate increases, leading to a decrease

Table 2. DKR of **2**, using **1** as a racemization catalyst and Novozym 435 as an acylating catalyst under various conditions[a]



2a **5a**

Entry	**3a** (mmol)	Novozym 435 (mg/mol)	Time (h)	**5a** (%)	ee[b] (%)
1	0.07[c]	11	23	99	>99
2	1.8	11	23	>99	>99
3	1.8	23	10	98	>99

[a] Reaction conditions: *rac*-**2a** (9 mmol), toluene (9 mL), isopropyl butyrate (18 mmol), catalyst **1** (0.009 mmol) and K_2CO_3 (3.8 mmol), Ar atmosphere, $T = 70$ °C, reduced pressure to ensure gentle reflux (approximately 200 mbar).

[b] Determined by chiral GC; calculated values.

[c] Reaction performed without addition of extra acetophenone; 0.07 mmol was present as an impurity in the starting alcohol, however.

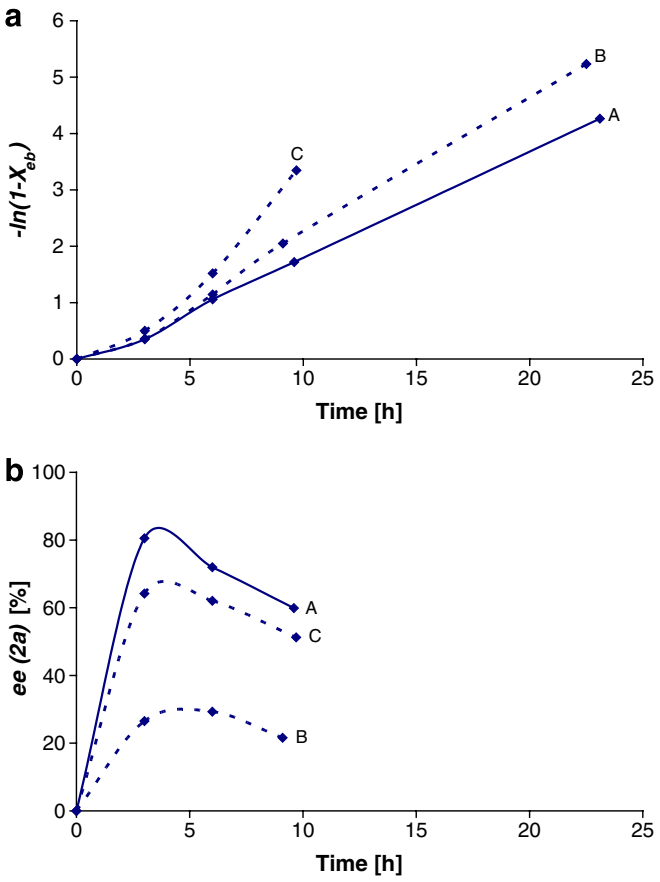


Figure 3. DKR of **2a** at 70 °C, with 0.1 mol % **1** as a racemization catalyst in the absence of acetophenone (A; Table 2, entry 1), in the presence of 1.8 mmol of **3a** (B; Table 2, entry 2) and in the presence of 1.8 mmol of **3a** with double the amount of enzyme (C; Table 2, entry 3). Toluene is used as the solvent. (a) Conversion based on enantiomeric balance (X_{eb}) versus reaction time. As first-order kinetics are obeyed, $-\ln(1 - X_{eb})$ is plotted, (b) ee of **2a** versus reaction time.

of the ee. Reaction in the presence of 1.8 mmol of **3a** shows a considerably lower ee implying faster racemization (Fig. 3b, entry B) and a rate-limiting enzymatic reaction. Therefore, the reaction was performed with double the amount of enzyme, resulting in faster transesterification and therefore a higher ee of **2a** during the reaction (Fig. 3b, entry C). Complete conversion with high ee of the product was achieved within 10 h (Table 2, entry 3; Fig. 3a, entry C).

In order to investigate the scope of the catalyst, an aliphatic secondary alcohol as well as aromatic alcohols bearing either an electron-releasing or an electron-withdrawing substituent on the phenyl ring were subjected to DKR. Furthermore, a heteroaromatic alcohol, 2-furyl ethanol, was tested in DKR with catalyst **1** (Table 3). From a commercial point of view, it is more attractive to use one ketone for all substrates. DKR reactions with ketones, other than the corresponding one, showed disappointing results, however. In addition, there are no advantages with respect to the isolation of the product as a result of transfer-hydrogenation between ketone and substrate. For this reason, the ketone corresponding to the substrate was used for each DKR.

DKR of 2-octanol **2b** gave a high yield and high ee within 10 h when 2-octanone **3b** was added. However, the amount of complex **1** was increased by a factor 4 and the amount of Novozym 435 was decreased by a factor 4, when compared to the DKR of **2a** in the presence of ketone. In the absence of **3b**, a considerably lower rate of reaction was obtained (Table 3, entry 4).

α-Methyl-4-(trifluoromethyl)benzyl alcohol **2c** (Table 3, entry 5), a substrate bearing an electron-withdrawing substituent on the phenyl ring, gave a high yield with excellent ee. For this DKR, a slightly longer reaction time of 30 h and double the amount of enzyme were required, when compared to the DKR of **2a** in the presence of ketone.

An aromatic alcohol bearing an electron-releasing substituent on the ring, α-methyl-4-methoxybenzyl alcohol **2d**, was also successfully converted into the enantiomerically pure butyrate ester. A slightly longer reaction time was required (Table 3, entry 6).

Finally, the DKR of the heteroaromatic 1-(2-furyl)ethanol **2e** was investigated (Table 3, entry 7). DKR of this substrate was complete after 23 h, resulting in a poor ee of 79%, however. Experiments with increased loading of racemization catalyst **1** did not lead to higher ee values. Verzijl et al. described that DKR of this substrate in combination with isopropyl butyrate as the acylating agent resulted in limited enantioselectivity. Improved results were reported employing methyl phenylacetate as the acyl donor.[4g]

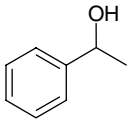
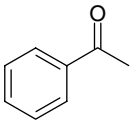
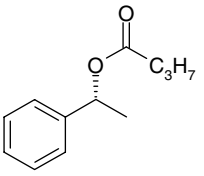
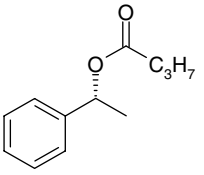
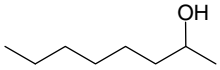
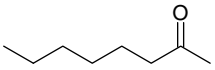
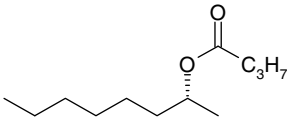
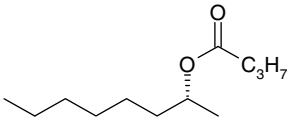
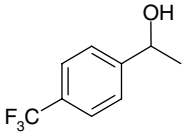
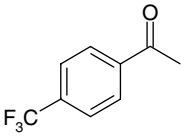
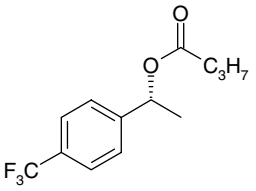
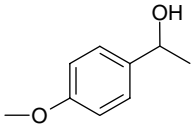
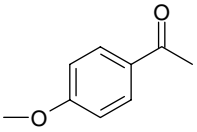
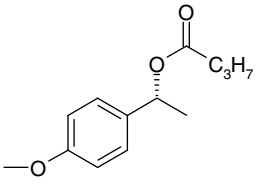
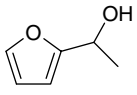
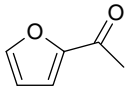
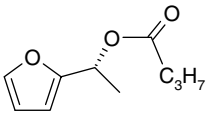
3. Conclusions

Dinuclear ruthenium complex **1**, bearing tetrafluorosuccinate and (*rac*)-BINAP ligands, was successfully applied in the DKR of various secondary alcohols.

The DKR of (*rac*)-**2a** with isopropyl butyrate as the acyl donor and Novozym 435 as the enzyme was performed effectively at 70 °C when 0.10 mol % of complex **1** was used as the racemization catalyst. Activation of the Ru catalyst with K_2CO_3 was necessary. Reaction in the presence of ketone was complete within 10 h with an excellent ee of the product (>99%). Without ketone, complete reaction was achieved in 23 h, giving an ee >99% as well.

Besides the aromatic alcohol **2a**, four other substrates were shown to undergo the DKR successfully, using complex **1** as the racemization catalyst. Those substrates represent an aliphatic secondary alcohol (2-octanol), an aromatic alcohol bearing an electron-withdrawing substituent on the phenyl ring (α-methyl-4-(trifluoromethyl)benzyl alcohol), an aromatic alcohol bearing an electron-donating substituent on the ring (α-methyl-4-methoxybenzyl alcohol) and a heteroaromatic secondary alcohol (1-(2-furyl)ethanol). Addition of the ketone corresponding to the alcohol is beneficial for the stability of the active Ru-complex and hence for the reaction rate and yield.

Table 3. Dynamic kinetic resolution of various racemic alcohols[a]

Entry	Alcohol	Ketone (mmol)	Time (h)	Product	Yield[b,c] (%)	ee[b] (%)
1	 **2a**	 **3a** (1.8 mmol)	10 23	 **5a**	98 >99	>99 >99
2		No ketone[d]	10 24	 **5a**	95 >99 (87)	>99 >99
3[e]	 **2b**	 **3b** (1.6 mmol)	10 23	 **5b**	99 >99	98 98
4[e]		No ketone	23	 **5b**	86	87
5[f]	 **2c**	 **3c** (1.6 mmol)	30	 **5c**	96 (79)[g]	>99
6	 **2d**	 **3d** (1.5 mmol)	31	 **5d**	98 (63)[g]	98
7	 **2e**	 **3e** (1.4 mmol)[h]	23	 **5e**	98	79

[a] Reaction conditions: complex **1** (0.1 mol %), Novozym 435 (0.2 g), K_2CO_3 (0.5 g), alcohol (9 mmol), isopropyl butyrate (18 mmol) and corresponding ketone were stirred in toluene (9 mL) under an argon atmosphere at 70 °C at reduced pressure (200 mbar).

[b] Determined by chiral GC; calculated values.

[c] In parenthesis: isolated yield.

[d] Reaction performed without addition of extra ketone, 0.07 mmol of ketone is present as an impurity in the starting alcohol, however.

[e] Novozym 435: 0.05 g; Ru-catalyst: 0.4 mol %.

[f] Novozym 435: 0.4 g.

[g] Product not separated from ketone; calculated yield.

[h] Ketone (1.4 mmol) was added in advance. Immediately at the start of the reaction this amount reduced to 0.4 mmol, however. Most likely, this can be attributed to transfer hydrogenation between 2-furyl ketone and isopropanol, which is simultaneously distilled from the reaction mixture.

4. Experimental

4.1. General

All reactants were obtained from Aldrich, except for Novozym 435, which is obtained from Novozymes. Complex **1** was synthesized according to the literature.[8] Substrates were distilled before use. K_2CO_3 (−325 MESH, Aldrich, 347825) was used to activate complex **1**.

^{1}H NMR spectra were recorded on a Varian Mercury Vx 300 spectrometer (300 MHz) using $CDCl_3$ as solvent. Chiral gas chromatography (GC) was performed on a Shimadzu 6C-17A GC equipped with a Chrompack Chirasil-DEX CB (DF = 0.25) column and an FID. Samples were injected using a Shimadzu AOC-20i autosampler.

4.2. General procedure for the racemization of (*S*)-1-phenylethanol

A Schlenk tube was charged with (*S*)-1-phenylethanol (0.55 g, 4.5 mmol), complex **1** (2.15 mg, 0.0011 mmol) and toluene (4.5 mL) and then K_2CO_3 (0.2 g, 1.5 mmol) was added. At time $t = 0$, the Schlenk tube was inserted in an oil bath of the desired temperature. Small aliquots of reaction mixture were taken for GC analysis.

4.3. Racemization in the presence of ketone

The procedure was similar to that of the general racemization procedure, but with initial addition of the ketone.

4.4. General DKR procedure

Novozym 435 (0.10 g, 0,00034 mmol), complex **1** (0.018 g, 0.0093 mmol) and K_2CO_3 (0.5 g, 3.8 mmol) were dried in a Schlenk tube under vacuum overnight at 50 °C in the presence of P_2O_5. Under an Ar-atmosphere, the Schlenk tube was charged with toluene (9 mL), substrate (9 mmol) and isopropyl butyrate (18 mmol). The Schlenk tube was inserted in an oil bath at 73 °C at time $t = 0$. The reaction mixture was stirred at 70 °C for 23 h at a pressure of 200 mbar. Small aliquots of reaction mixture were taken for GC analysis. For preparative purposes, the reaction mixture was concentrated, filtered, washed with toluene and concentrated in vacuum to yield the crude product.

4.5. (*R*)-1-Phenylethyl butyrate 5a

Purification by Kugelrohr distillation provided (*R*)-1-phenylethyl butyrate **5a** as a colourless liquid with a yield of 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.95 (t, 3H, CH_3), 1.55 (d, 3H, CH_3), 1.63 (sextet, 2H, CH_2), 2.32 (t, 2H, CH_2), 5.92 (q, 1H, CH), 7.32 (5H, Ar–H). GC program: 10 min at 130 °C, 70 °C/min, 2 min at 200 °C. Retention times: (*R*)-1-phenylethanol: 5.9 min, (*S*)-1-phenylethanol: 6.2 min, tri-*tert*-butyl benzene: 9.7 min, (*R*)-1-phenylethyl butyrate: 8.9 min. $[\alpha]_D^{25} = +91.3$ (*c* 0.98, $CHCl_3$).

4.6. (*R*)-α-Methyl-4-(trifluoromethyl)benzyl butyrate 5c

Purification by Kugelrohr distillation provided (*R*)-1-α-methyl-4-(trifluoromethyl)benzyl butyrate **5c** as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.95 (t, 3H, CH_3), 1.55 (d, 3H, CH_3), 1.69 (sextet, 2H, CH_2), 2.35 (t, 2H, CH_2), 5.94 (q, 1H, CH), 7.48 (d, 2H, Ar–H2,6), 7.61 (d, 2H, Ar–H3,5). GC program: 35 min at 110 °C, 90 °C/min, 2 min at 200 °C. Retention times: trifluoromethyl acetophenone: 6.3 min, (*R*)-α-methyl-4-(trifluoromethyl)benzyl alcohol: 23.0 min, (*R*)-α-methyl-4-(trifluoromethyl)benzyl butyrate: 26.7 min, (*S*)-α-methyl-4-(trifluoromethyl)benzyl alcohol: 28.6 min.

4.7. (*R*)-α-Methyl-4-methoxybenzyl butyrate 5d

Purification by Kugelrohr distillation provided (*R*)-α-methyl-4-methoxybenzyl butyrate **5d** as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.95 (t, 3H, CH_3), 1.52 (d, 3H, CH_3), 1.69 (sextet, 2H, CH_2), 2.31 (t, 2H, CH_2), 3.80 (s, 3H, CH_3), 5.88 (q, 1H, CH), 6.89 (d, 2H, Ar–H3,5), 7.32 (d, 2H, Ar–H2,6). GC program: 20 min at 140 °C, 60 °C/min, 2 min at 200 °C. Retention times: 4-methoxy acetophenone: 8.2 min, (*R*)-α-methyl-4-methoxybenzyl alcohol: 10.8 min, (*S*)-α-methyl-4-methoxybenzyl alcohol: 11.5 min, (*S*)-α-methyl-4-methoxybenzyl butyrate: 20.0 min, (*R*)-α-methyl-4-methoxybenzyl butyrate: 20.7 min.

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9. For the reaction (*S*)-**2** ↔ (*R*)-**2**, with rate constants for the forward and reverse reaction, k_1 and k_{-1}, respectively, the mass balance for the (*S*)-enantiomer can be derived: $d[(S)\text{-}\mathbf{2}]/dt = -k_1\cdot[(S)\text{-}\mathbf{2}] + k_{-1}\cdot[(R)\text{-}\mathbf{2}]$. In case of racemization by an achiral catalyst $k_1 = k_{-1}$ by definition, which results in: $d[(S)\text{-}\mathbf{2}]/dt = k_1\cdot\{[(R)\text{-}\mathbf{2}] - [(S)\text{-}\mathbf{2}]\}$. Introducing $ee = \{[(S)\text{-}\mathbf{2}] - [(R)\text{-}\mathbf{2}]\}/\{[(S)\text{-}\mathbf{2}] + [(R)\text{-}\mathbf{2}]\}$ gives $d(ee)/dt = -2\cdot k_1\cdot ee$. The conversion is defined as: $X = 1 - (ee/ee_0)$, which can be rewritten as $ee = \{(1 - X)/ee_0\}$. Now it can be derived that $dX/dt = 2\cdot k_1\cdot(1 - X)$ or $dX/(1 - X) = 2\cdot k_1\cdot dt$, which is consistent with overall first-order kinetics.
10. Reactions were performed at 100 °C as the strongest effect of addition of acetophenone was obtained at this temperature.