

# Removal of the acyl donor residue allows the use of simple alkyl esters as acyl donors for the dynamic kinetic resolution of secondary alcohols

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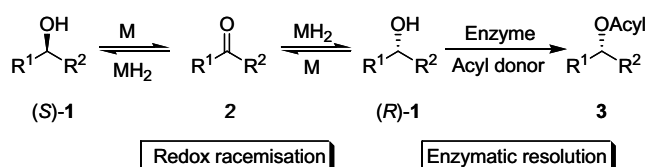
**Abstract**—The dynamic kinetic resolution of secondary alcohols using a lipase and a ruthenium catalyst as developed by Bäckvall required some improvements to make it suitable for its use in an industrial process. The use of *p*-chlorophenyl acetate as acyl donor is not desirable in view of the toxicity of the side product. We herein report that simple alkyl esters can be used as acyl donors if the alcohol or ketone residue formed during the enzymatic acylation is continuously removed during the reaction. The addition of a ketone speeds up the racemisation process and allowed us to reduce the amounts of enzyme and ruthenium catalyst. The scope of this method was explored and a suitable range of acyl donors found. Various benzylic and aliphatic alcohols were reacted using isopropyl butyrate or methyl phenylacetate as acyl donor and in most cases the ester was isolated in >95% yield and 99% ee. Furthermore, it was demonstrated that the alcohol by-products of the enzymatic resolution could be used as the hydrogen source in the asymmetric reductive transesterification of ketones.

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## 1. Introduction

Optically active secondary alcohols are important building blocks for pharmaceuticals, agrochemicals and liquid crystals. Relevant methods for their preparation from readily available ketones are asymmetric processes such as catalytic hydrogenations,<sup>1a</sup> hydrosilylations,<sup>1b</sup> transfer hydrogenations,<sup>1a,2</sup> hydroborations<sup>3</sup> and bio-reductions.<sup>4</sup> Alternatively, enantiomerically pure secondary alcohols can also be obtained by the kinetic resolution<sup>5</sup> of racemic mixtures using either asymmetric catalytic oxidation<sup>6</sup> or chiral chromatography. High enantioselectivity in kinetic resolutions can also be achieved by enzymatic transesterification.<sup>7</sup> However, an important drawback of kinetic resolutions is the intrinsically low maximum theoretical yield of 50%. In some special circumstances, it is possible to obtain a theoretical yield of 100% by carrying out substrate racemisation under the resolution conditions. Such processes constitute a very special subclass of kinetic resolution reactions known as dynamic kinetic resolution (DKR).<sup>8</sup> The DKR of secondary alcohols by combining

an enzymatic resolution with a transition metal-mediated redox racemisation is arguably one of the best methods to produce optically active esters<sup>9</sup> (Scheme 1).

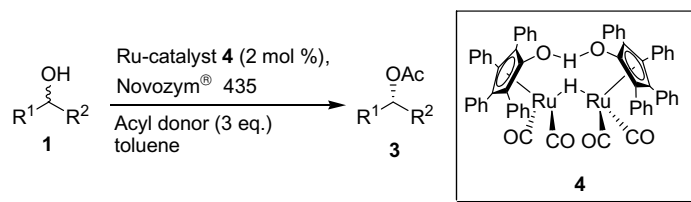


Scheme 1. The dynamic kinetic resolution of secondary alcohols.

In this concept, the two enantiomers of the substrate are equilibrated by a redox reaction with the continuous removal of one of the enantiomers using stereoselective enzymatic acylation. Hydrolysis of the optically active ester produced will give the corresponding enantiopure secondary alcohol.

This concept was first proven by Williams and co-workers.<sup>10</sup> Bäckvall et al. realised a significant breakthrough by identifying a compatible catalyst combination of immobilised lipase B from *C. antarctica* (commercially traded as Novozym® 435) for the resolution and a ruthenium-based racemisation catalyst, originally developed

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Scheme 2.

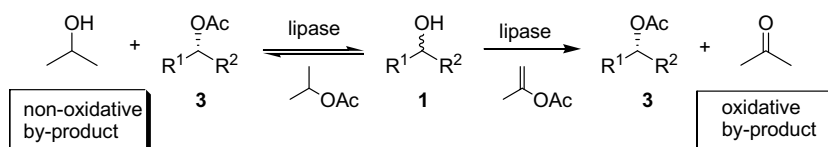
by Shvo **4**, which turned out to be very effective for the DKR of secondary alcohols (Scheme 2).<sup>11</sup> However, the use of vinyl acetate or isopropenyl acetate as the acyl donor was identified as being disadvantageous due to the formation of acetaldehyde or acetone, respectively, which caused undesired side reactions. Employing *p*-chlorophenyl acetate as the acyl donor solved the problem, releasing *p*-chlorophenol as a non-interfering residue.

A number of patents have since been published in this field.<sup>12</sup> For environmental and economic reasons, *p*-chlorophenyl acetate has to be replaced by an alternative acyl donor. For industrial applications, only simple acyl donors that are available in bulk are of interest. However, depending on the acyl donor, kinetic resolution can lead to by-products, which in the presence of a redox racemisation catalyst, are either non-oxidative or oxidative, as illustrated in Scheme 3.

Kinetic resolution with isopropyl acetate generates isopropanol. Isopropanol acts as a hydrogen source, effectively creating reductive conditions in the presence of a redox racemisation catalyst (non-oxidative). Unfortunately, problems arise due to the reversibility of the transesterification with isopropanol in the enzymatic resolution and therefore the reaction ends in equilibrium. The solution for this problem was the introduction of enol-esters as acylating agents, which lead to irreversible transesterifications because of the formation of aldehydes or ketones. However, aldehydes and ketones are hydrogen acceptors and act as oxidants in the presence of a redox racemisation catalyst (oxidative). As demonstrated with *p*-chlorophenyl acetate, enzymatic kinetic resolution reactions can be shifted towards the product by the use of irreversible acyl donors, which release non-interfering by-products.<sup>11a,b,d</sup> Thus, chemically speaking *p*-chlorophenyl acetate is an excellent acylating agent since it circumvents the above problems. However, it generates the toxic side product *p*-chlorophenol, thus making this compound less desirable from an environmental perspective. To date, only a few examples of simple esters have been reported. A practical method

was described starting from ketones in ethyl acetate. Molecular hydrogen was employed in the hydrogenation of the pro-chiral ketone to racemic alcohol in combination with a DKR in ethyl acetate (acyl donor for enzymatic transesterification) using the same ruthenium racemisation catalyst.<sup>13</sup> Over a period of 96 h, the reaction mixture was concentrated to one-third in volume every 24 h followed by volume replenishment with fresh ethyl acetate. Slow transesterification was recognised as a major drawback in the use of ethyl acetate. Recently, Park et al. reported an efficient DKR using isopropenyl acetate as acyl donor.<sup>14</sup> For this purpose, a novel, more active catalyst was developed. A low degree of alcohol oxidation was achieved without the aid of a ketone as co-catalyst. Unfortunately, high catalyst loadings (up to 8 mol % Ru) are necessary to perform DKR at room temperature with reasonable yields. Also Bäckvall et al. have recently reported that the use of  $(\text{Ph}_5\text{Cp})\text{Ru}(\text{CO})_2\text{X}$  (X = Cl, Br) allows the use of isopropenyl acetate, but 5 mol % of this ruthenium catalyst was needed for a fast rate.<sup>11c</sup> Reasonable yields of acylated diols could be obtained by the same group with a combination of isopropenyl acetate and 4 mol % of the Shvo catalyst **4** using Lipase B from *Candida antartica*, particularly in the presence of hydrogen to suppress ketone formation.<sup>11d</sup>

We have found that selective distillation of the residue of the acyl donor after enzymatic conversion in DKR is a convenient method to overcome the described problems,<sup>12a,b</sup> giving the optically active esters in high yields and ee's at low catalyst loadings. In the case of an enzymatic resolution leading to a non-oxidative by-product, selective removal of the released volatile alcohol shifts the equilibrium of the reaction towards the desired product. Likewise, volatile oxidant by-products can be removed when enol-esters are employed. Herein, we report our results concerning the DKR of (*RS*)-1-phenylethanol **1a** using standard esters as acylating agents. Furthermore, we also report the DKR of a number of aliphatic and benzylic secondary alcohols in a standardised procedure with isopropyl butyrate or methyl phenylacetate as acylating agent.

Scheme 3. Enzymatic resolution leading to non-oxidative or oxidative by-products (the remaining (*S*)-alcohol has been omitted for clarity).

## 2. Results and discussion

### 2.1. DKR with simple esters

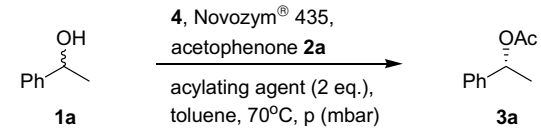
Esterification of **1a** was carried out using lipase B from *C. antarctica* (Novozym<sup>®</sup> 435) as enantioselective acylating catalyst, Shvo's ruthenium catalyst **4** as redox racemisation catalyst, isopropenyl acetate as acylating agent and toluene as solvent. In order to avoid competitive distillation of the acyl donor, distillation conditions had to be optimised for each specific acyl donor separately, as illustrated for isopropenyl acetate in Table 1.

In order to determine optimal DKR conditions, 1-phenylethanol **1a** (8 mmol) was treated with isopropenyl acetate (16 mmol) at 70 °C under distillation conditions at various pressures in the presence of acetophenone **2a** as ketone co-catalyst, Novozym<sup>®</sup> 435 and racemisation catalyst **4**. As can be seen in Table 1, relatively low yields were achieved at pressures below 210 mbar (entries 1–2) due to the loss of isopropenyl acetate. A high yield and ee was obtained by distillation at 210 mbar in the presence of 25 mol % **2a** (entry 3). In this particular case, less oxidation was observed in comparison with DKR under more rigorous distillation conditions, indicating that another oxidation mechanism is involved when carrying out distillation at lower pressures. Presumably, a catalytic dehydrogenation process becomes active when acetone and the acyl donor have completely disappeared. Oxidation was kept to a minimum at 210 mbar and only a trace of **1a** remained in the reaction mixture. The reaction became rather slow upon further reduction of the amount of catalysts (entries 4 and 5). Prolonging the reaction from 15 to 24 h at atmospheric pressure gave **3a** in 95% yield and 99% ee (entry 5). Reducing the amount of co-catalyst **2a** to 10 mol % (entry 6), detrimentally affected the reaction speed and as a consequence we had to run the reaction for 22 h in order to get a higher yield.

In a similar manner to that described for isopropenyl acetate, a variety of potentially inexpensive, simple acylating agents was studied in the DKR. By varying only

the distillation pressure, the DKR conditions found for the reaction with isopropenyl acetate were also shown to be suitable for the DKR with other acylating agents. The chemical yields and enantioselectivities observed using these acylating agents are summarised in Table 2.

**Table 2.** DKR with various simple esters as acylating agent<sup>a</sup>

					
Entry	Acylating agent	<i>P</i> (mbar)	<i>t</i> (h)	Ester (%)	Ee (%)
1	Isopropenyl acetate	210	22	<b>3a</b> (97)	98
2 <sup>b</sup>	Isopropyl acetate	220	23	<b>3a</b> (99)	97
3 <sup>c</sup>	Isopropyl acetate	220	24	<b>3a</b> (63)	92
4	Ethyl acetate <sup>d</sup>	290	28	<b>3a</b> (83)	99
5	Methyl butyrate	205	24	<b>5a</b> (>99)	>99
6	Isopropyl butyrate	190	24	<b>5a</b> (>99)	99
7	Isopropyl butyrate <sup>e</sup>	65	18	<b>5a</b> (96)	99
8	Methyl phenylacetate	190	24	<b>6a</b> (91)	>99

<sup>a</sup> Reaction conditions: *rac*-**1a** (8 mmol), toluene (10 mL), acylating agent (16 mmol), **2a** (0.8 mmol), catalyst **4** (0.04 mmol) and Novozym<sup>®</sup> 435 (60 mg), N<sub>2</sub> atmosphere, *T* = 70 °C, Δ*p* (as indicated in table).

<sup>b</sup> Over first 6 h 245 mbar, then slowly to 220 mbar.

<sup>c</sup> Without **2a**.

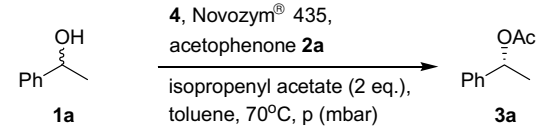
<sup>d</sup> Acyl donor (3 equiv).

<sup>e</sup> *o*-Xylene as solvent.

Completely oxidation-free conditions will never be achieved with isopropenyl acetate. Even at optimal conditions at least a trace amount of ketone derived from the substrate will be present in the reaction mixture. Therefore, the exclusion of the ketone effect is impossible for isopropenyl acetate.

We also wished to study the influence of the ketone co-catalyst on the racemisation rate. DKR without a ketone co-catalyst is preferred, since the isolation of

**Table 1.** DKR of **1a** employing isopropenyl acetate as acylating agent<sup>a</sup>

							
Entry	<b>2a</b> (mol %)	Novozym 435 (mg/mol)	<b>4</b> (mol %)	Pressure (mbar)	Time (h)	<b>3a</b> (%)	Ee (%)
1	25	60	0.5	200	15	64	98
2	25	60	0.5	205	15	91	98
3	25	60	0.5	210	15	98	98
4	25	30	0.25	210	15	78	99
5 <sup>b</sup>	25	30	0.25	215	15	91	99
6	10	60	0.5	210	24	95	99
					15	94	98
					22	97	98

<sup>a</sup> Reaction conditions: *rac*-**1a** (8 mmol), toluene (10 mL), isopropenyl acetate (16 mmol), **2a**, catalyst **4** and Novozym<sup>®</sup> 435 (see table for further details), N<sub>2</sub> atmosphere, *T* = 70 °C, Δ*p*.

<sup>b</sup> Distillation was terminated after 15 h.

the product is less complicated. Generating isopropanol by enzymatic transesterification (non-oxidative by-product), isopropyl acetate was investigated in the DKR under permanent distillation conditions in the absence of ketone as co-catalyst. Unfortunately, DKR of **1a** without the aid of **2a** was accompanied by a dramatic negative effect on the racemisation rate and as a consequence a low yield and disappointing enantiomeric excess was obtained (entry 3). In comparison with isopropyl acetate, the use of the more volatile ethyl acetate furnished **3a** in lower yields. Selective distillation of ethanol becomes rather difficult, since the boiling points of ethyl acetate and ethanol are very close.

Using methyl butyrate allowed us to lower the pressure a bit further and this, in combination with the more volatile methanol, resulted in a more effective DKR. Since methanol and isopropanol have reductive properties, almost complete conversion of **1a** took place with excellent ee when the reaction was carried out with methyl butyrate or isopropyl butyrate, respectively (entries 5 and 6).

Using high boiling esters as acylating agents allowed us to further enhance the distillation conditions (entries 6–8). It was also anticipated that the boiling point difference between the reaction medium and the volatile by-products could be improved using a high boiling solvent as well. In contrast, however, replacing toluene as the solvent of choice by *o*-xylene did not bear out these expectations significantly (entry 7). In a 24 h reaction time, complete conversion was obtained in *o*-xylene as well.

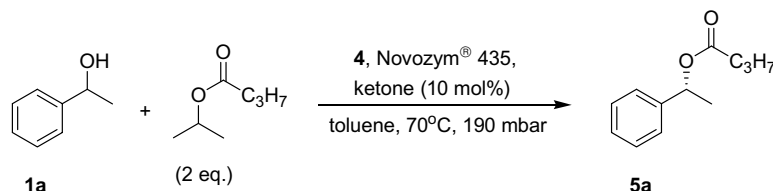
The utilisation of acylating agents with different acyl chain bulkiness is also crucial for enhancing the enantioselectivity. A suitable acyl donor for many enzymatic transformations is methyl phenylacetate and this reagent is of particular interest when enantioselectivities in enzymatic transesterifications need to be improved (entry 8).

## 2.2. Other ketones as co-catalyst

In general, a DKR with catalyst **4** needs the aid of a ketone as co-catalyst for effective racemisation. The effectiveness of the co-catalyst strongly depends on the equilibration conditions between the ketone (co-catalyst) and the substrate alcohol, which in turn is affected by the difference in oxidation potential of the co-catalyst and the ketone derived from the substrate alcohol.<sup>15</sup> More specifically, the best racemisation conditions are obtained in the presence of the ketone derived from the substrate alcohol. For practical reasons, we prefer to have a general methodology for all types of substrates. To fulfil this purpose, we investigated benzophenone and 2,4-dimethyl-3-pentanone as possible alternative co-catalysts in the DKR of **1a** (Table 3). At the beginning of the reaction, **1a** partially oxidises to acetophenone **2a** and the co-catalyst reduces to the corresponding alcohol resulting in the temporary storage of hydrogen in the co-catalyst. Steric bulk in co-catalyst side chains avoids transformation of the produced co-catalyst alcohol to ester by the enzyme. In the final stage of the DKR process, the co-catalyst alcohol will deliver back its hydrogen to the substrate ketone giving racemic substrate alcohol and in combination with the enzymatic acylation will approach the theoretical yield of 100% without formation of interfering side products.<sup>16</sup>

In the case, when acetophenone **2a** was used as racemisation co-catalyst, it was partially reduced by transfer hydrogenation with isopropanol stemming from the enzymatic reaction resulting in a slightly higher yield than the theoretical one (entry 1). Surprisingly, a high yield and enantiomeric excess were achieved with methyl butyrate in the presence of 2,4-dimethyl-3-pentanone (entry 2). Optically active butyrate ester **3a** was obtained in 97% yield and 99% ee in 40 h. Since the performance of both, 2,4-dimethyl-3-pentanone and benzophenone, as co-catalyst in DKR is nearly the same (entries 3 and 4), we decided to employ 2,4-dimethyl-3-pentanone as the co-catalyst of choice. In contrast to benzophen-

**Table 3.** Different ketones as co-catalyst in the DKR of **1a**<sup>a</sup>



Entry	Co-catalyst	<i>t</i> (h)	<b>3a</b> (%)	Ee (%)
1 <sup>b</sup>	Acetophenone <b>2a</b>	24	102	99
2 <sup>c</sup>	2,4-Dimethyl 3-pentanone	24	90	99
		40	97	99
3	2,4-Dimethyl 3-pentanone	40	95	99
4	Benzophenone	40	95	99

<sup>a</sup> Reaction conditions: *rac*-**1a** (8 mmol), toluene (10 mL), *iso*-propyl butyrate (16 mmol), co-catalyst (0.8 mmol), catalyst **4** (0.04 mmol) and Novozym<sup>®</sup> 435 (60 mg), N<sub>2</sub> atmosphere, *T* = 70 °C, *p* → 190 mbar.

<sup>b</sup> Complete conversion of **1a** in conjunction with partial transfer hydrogenation of **2a**.

<sup>c</sup> Methyl butyrate used as acyl donor at 205 mbar.

one, 2,4-dimethyl-3-pentanone can be easily removed by distillation at the end of the reaction.

### 2.3. Combined transfer hydrogenation and DKR

Since most racemic alcohols are prepared from the corresponding ketones we were interested to test the possibility of combining a transfer hydrogenation and a DKR in a domino reaction. This is indeed possible according to the process shown in Scheme 4.

The reaction was initiated by the addition of a substoichiometric amount (15 mol %) of *iso*-propanol generating **1a** by catalytic transfer hydrogenation at atmospheric pressure catalysed by **4**. In the presence of lipase, enantioselective acylation of **1a** with isopropyl butyrate afforded the corresponding butyrate ester **5a** with generation of isopropanol as by-product. At the same time, the produced *iso*-propanol was used as hydrogen source for further reduction of ketone. At atmospheric pressure however, ketone **2a** was converted to optically active ester **5a** in only 10% yield in 4 h, indicating that the system equilibrates with acetone and isopropanol. Continuing the reaction by selective distillation of acetone at 300 mbar shifts the equilibrium furnishing **5a** in 50% yield and >99% ee after 68 h. In this experiment it has been shown for the first time that starting with only a substoichiometric amount of *iso*-propanol, a reasonable yield can be obtained for the conversion of a ketone to an optically active ester by combining a catalytic transfer hydrogenation/racemisation and an enzymatic resolution that produces a hydrogen source as by-product. Unfortunately, distillation of acetone is accompanied by removal of isopropanol to a certain extent, leading to incomplete conversion.

### 2.4. DKR of secondary alcohols with isopropyl butyrate

The scope of our system is illustrated by the transformation of a wide range of different secondary alcohols. Using the conditions established in the above studies, both benzylic and aliphatic secondary alcohols **1a–m** were converted to the corresponding optically active butyrate esters **5a–m** (Table 4). All of the reactions shown were performed with reagent grade, unpurified materials.

Substituents on the aromatic ring did not affect the results significantly (entries 1–7), nor did the prolongation of the alkyl chain adjacent to the carbinol group from

**Table 4.** DKR of benzylic and aliphatic secondary alcohols **1a–m**<sup>c</sup>

**1a** R<sup>1</sup>=Ph; R<sup>2</sup>=Me

**1b** R<sup>1</sup>=Ph; R<sup>2</sup>=Et

**1c** R<sup>1</sup>=*p*-ClC<sub>6</sub>H<sub>4</sub>; R<sup>2</sup>=Me

**1d** R<sup>1</sup>=*p*-OMeC<sub>6</sub>H<sub>4</sub>; R<sup>2</sup>=Me

**1e** R<sup>1</sup>=*m*-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; R<sup>2</sup>=Me

**1g** R<sup>1</sup>=*p*-FC<sub>6</sub>H<sub>4</sub>; R<sup>2</sup>=Me

**1h** R<sup>1</sup>=PhOCH<sub>2</sub>; R<sup>2</sup>=Me

**1i** R<sup>1</sup>=2-furyl; R<sup>2</sup>=Me

**1k** R<sup>1</sup>=*n*-C<sub>6</sub>H<sub>13</sub>; R<sup>2</sup>=Me

**1l** R<sup>1</sup>=*t*-Bu; R<sup>2</sup>=Me

**1m** R<sup>1</sup>=*c*-C<sub>6</sub>H<sub>11</sub>; R<sup>2</sup>=Me

**1f** n=2

**1j** n=1

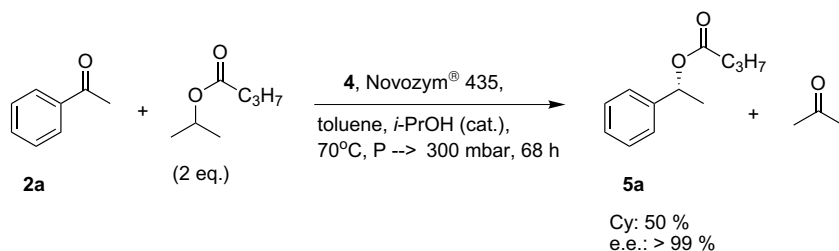
Entry	Substrate	<b>4</b> (mol %)	Enzyme (mg)	<i>t</i> (h)	<b>5a–m</b> <sup>a</sup> (%)	Ee (%)
1	<b>1a</b>	0.5	60	40	96	99
2	<b>1b</b>	0.5	60	40	94	>99
3	<b>1c</b>	0.5	60	40	96	99
4	<b>1d</b>	0.5	60	40	93	>99
5	<b>1e</b>	1	60	40	91	>99
6	<b>1f</b>	0.5	60	40	90	>99
				68	92	>99
7	<b>1g</b>	0.5	60	40	91	99
				68	98	99
8	<b>1h</b>	1	10	40	75	84
9	<b>1i</b>	0.5	20	40	87	95
10	<b>1j</b>	0.5	30	40	87	99
11	<b>1k</b>	0.5	20	40	90	95
12	<b>1l</b>	0.5	120	40	75 <sup>b</sup>	97
13	<b>1m</b>	0.5	60	40	97	>99

<sup>a</sup> GC assay yield.

<sup>b</sup> Reaction was carried out at 210 mbar (*p* → 210 mbar in order to suppress distillation of **1l**).

<sup>c</sup> Reaction conditions: *rac*-alcohol (8 mmol), toluene (10 mL), *iso*-propyl butyrate (16 mmol), 2,4-dimethyl-3-pentanone (0.8 mmol), catalyst **4** and Novozym<sup>®</sup> 435 (see table for further details), N<sub>2</sub> atmosphere, *T* = 70 °C, *p* → 190 mbar.

methyl to ethyl **1b** (entries 1–2). To our surprise, we found that the ratio between the rates of the catalytic redox racemisation and the enzymatic acylation were very similar for all benzylic substrates. Prolonging of the reaction time from 40 to 68 h did not result in a significant higher yield of **5f** (entry 6). In contrast, **1g** was almost completely converted to the product by continuation of the DKR for a longer period (entry 7). For the other substrates, optimisation of the catalyst amounts for each substrate was essential for a high level of enantioselectivity (entries 8–12). In sharp contrast to previous reports,<sup>11a</sup> Novozym<sup>®</sup> 435 appeared to have a



Scheme 4.

lower stereoselectivity for **1h**. Unfortunately, attempts to improve the selectivity by examining the balance between the enzyme and racemisation catalyst did not lead to enhancement of the enantioselectivity (entry 8).

Heteroaromatic substrate alcohol **1i** bearing an oxygen atom on the aromatic ring, is an excellent substrate for the enzymatic reaction. Diminishing the enzyme amount was necessary to preserve the enantioselectivity of the reaction (entry 9). For the same reason, the enzyme reaction was retarded by lowering the enzyme quantity for the cyclic aromatic substrate **1j** and 2-octanol **1k**.

The remaining alcohol with a low enantiomeric excess and the corresponding ketone are present in the final reaction mixture in different ratios for all substrates tested. The ratio of alcohol and ketone depended on the equilibration conditions, which in turn depended on the oxidation potential of both the substrate ketone and 2,4-dimethyl-3-pentanone co-catalyst.

Following the standard procedure for **1l**, the enzyme reaction became slow due to the extra steric bulk on the substrate. An acceptable reaction speed was achieved by doubling the amount of lipase. Unfortunately, standard distillation conditions gave less than the expected yield due to substrate distillation. Repeating the reaction at a higher distillation pressure afforded **5l** in only 75% yield.

Substrate alcohol **1m** approximately resembles the steric bulk of **1a** inducing a high enantioselectivity of the enzyme with a similar catalyst ratio. 1-Cyclohexylalcohol **1m** represents a successful example of the DKR of secondary aliphatic alcohols. Alcohol **1m** was resolved in remarkably good yield and excellent enantiomeric excess (entry 13).

As outlined before, improving the enantioselectivity can be accomplished by selection of the proper acylating agent. In the next set of experiments, it is demonstrated that for **1h**, **1i** and **1k**, the insufficient enantioselectivities obtained with isopropyl butyrate could be enhanced through the use of methyl phenylacetate (Table 5).

For substrate **1a**, the DKR was also demonstrated with methyl phenylacetate under the standard conditions developed for isopropyl butyrate (entry 1). Surprisingly, the simple replacement of isopropyl butyrate as the acyl donor resulted in a tremendous improvement in the enantioselectivity of **1h**. As recently pointed out in the literature, the enantioselectivity of 1-(2-furyl) ethanol **1i**, an interesting chiral building block, could also be improved by the application of other lipases using isopropenyl acetate as an acylating agent.<sup>17</sup> However, with Novozym<sup>®</sup> 435 acting as lipase, it gave a good performance in the DKR's with methyl phenylacetate as acylating agent affording the product ester in high yield and enantiomeric excess. The enantioselectivity of the resolution of 2-octanol **1k** using methyl phenylacetate as acylating agent could also be improved.

### 3. Conclusion

The low cost and lack of appreciable toxicity of common alkyl esters makes their use as acyl donors both economically and environmentally attractive.<sup>18</sup> For the first time we have demonstrated a very efficient DKR of secondary alcohols using non-excessive amounts (2 equiv) of simple esters as acylating agents together with selective distillation of the acyl donor residue. The DKR is very effective with respect to catalyst loading and requires only small quantities of Ru-catalyst **4** (up to 0.25 mol %) and Novozym<sup>®</sup> 435. Furthermore, we have reported the potential use of the liberated alcohol residue as a mild hydrogen source in the reduction of ketones followed by stereoselective transesterification for the synthesis of optically active esters.

An important drawback of catalyst **4** in the DKR is the use of ketone as co-catalyst, which complicates the isolation of the product. Furthermore, Ru<sub>3</sub>CO<sub>12</sub> the raw material for the preparation of the racemisation catalyst is not readily available in large quantities at acceptable costs. In due course, we will report the solutions we have found for these remaining problems, including a simple isolation of the product, alternative catalysts and catalyst recovery.<sup>12a</sup>

## 4. Experimental

### 4.1. General

Solvents, substrates **1a–m**, acylating agents (simple esters), ketones, Ru<sub>3</sub>CO<sub>12</sub> and tetraphenylcyclopentadienone were obtained commercially and used without further purification. Novozym<sup>®</sup> 435 is commercially available immobilised *Candida Antartica* Lipase B.

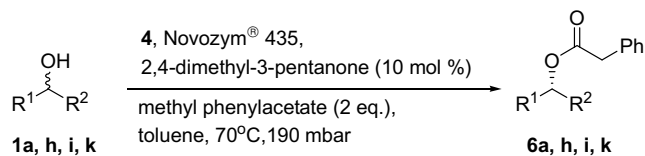
### 4.2. [(C<sub>4</sub>Ph<sub>4</sub>COHOCC<sub>4</sub>Ph<sub>4</sub>)(μ-H)][(CO)<sub>4</sub>Ru<sub>2</sub>]**4**<sup>19</sup>

Catalyst **4** was prepared from Ru<sub>3</sub>CO<sub>12</sub> and tetraphenylcyclopentadienone according to the literature.<sup>19</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) –18.3 (s, Ru-H), 7.1 (m, phenyls), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 88.1 (s), 103.9 (s), 127.2 (d), 127.9 (d), 128.1 (d), 128.2

Table 5. DKR using methyl phenylacetate as acyl donor<sup>a</sup>

Entry	Substrate	<b>4</b> (mol %)	Enzyme (mg)	Yield (%)	Ee (%)
1	<b>1a</b>	0.5	60	93	>99
2	<b>1h</b>	1	20	88	>99
3	<b>1i</b>	0.5	30	94	99
4	<b>1k</b>	0.5	20	84	>99

<sup>a</sup> Reaction conditions: *rac*-alcohol (8 mmol), toluene (10 mL), methyl phenylacetate (16 mmol), 2,4-dimethyl-3-pentanone (0.8 mmol), catalyst **4** and Novozym<sup>®</sup> 435 (see table for further details), N<sub>2</sub> atmosphere, T = 70 °C, p → 190 mbar, 40 h.



(d), 130.6 (s), 131.0 (s), 131.4 (d), 132.4 (d), 154.6 (s), 201.2 (s).

#### 4.3. General procedure for the dynamic kinetic resolution of secondary alcohols 1a–m

A mixture of *rac*-alcohol **1** (8 mmol), acyl donor (16 mmol), 2,4-dimethyl-3-pentanone (91.4 mg, 0.8 mmol), Novozym<sup>®</sup> 435 and **4** in toluene (10 mL) was degassed with dry nitrogen at room temperature. The DKR was carried out under stirring at 70 °C and distillation of the acyl donor residue conducted by a slow decrease of the pressure to 195 mbar over a period of 1 h. The ees of the alcohol and ester, as well as the conversion of the racemic alcohol, were monitored by chiral GC analysis using a CP-Chirasil-DEX CB (25 m × 0.25 mm) column with the exception of ester **6i**. The ee of **6i** was determined by hydrolysis of the ester and ee determination of the corresponding alcohol. For the ee determination of **1k** and **1m**, the alcohol was converted to the acetate ester by derivatisation with acetic anhydride in the presence of DMAP as acylation catalyst.

#### 4.4. (*R*)-1-Phenylethyl butyrate 5a

Purification by flash chromatography (hexane/EtOAc) afforded (*R*)-1-phenylethyl butyrate **5a** (1.28 g, 83%) as a colourless liquid.  $[\alpha]_{\text{D}}^{20} = +92.6$  (*c* 0.99, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 0.95 (t, 3H, CH<sub>3</sub>), 1.55 (d, 3H, CH<sub>3</sub>), 1.64 (sextet, 2H, CH<sub>2</sub>), 2.32 (t, 2H, CH<sub>2</sub>), 5.91 (q, 1H, CH), 7.32 (m, 5H, Ph); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 14.0 (CH<sub>3</sub>), 18.9 (CH<sub>2</sub>), 22.6 (CH<sub>3</sub>), 36.9 (CH<sub>2</sub>), 72.4 (CH), 126.4 (CH), 128.1 (CH), 128.8 (CH), 142.3 (C), 173.3 (C).

#### 4.5. (*R*)-1-Phenylpropyl butyrate 5b

Purification by flash chromatography (hexane/EtOAc) afforded (*R*)-1-phenylpropyl butyrate **5b** (1.39 g, 84%) as a colourless liquid.  $[\alpha]_{\text{D}}^{20} = +92.1$  (*c* 1.01, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 0.92 (m, 6H, 2CH<sub>3</sub>), 1.66 (sextet, 2H, CH<sub>2</sub>), 1.88 (m, 2H, CH<sub>2</sub>), 2.33 (t, 2H, CH<sub>2</sub>), 5.69 (t, 1H, CH), 7.31 (m, 5H, Ph); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 10.3 (CH<sub>3</sub>), 14.0 (CH<sub>3</sub>), 18.9 (CH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 36.9 (CH<sub>2</sub>), 77.4 (CH), 126.9 (CH), 128.1 (CH), 128.7 (CH), 141.1 (C), 173.4 (C).

#### 4.6. (*R*)-1-(*p*-MeO-phenyl) ethyl butyrate 5d

Purification by flash chromatography (hexane/EtOAc) afforded (*R*)-1-(*p*-MeO-phenyl) ethyl butyrate **5d** (1.42 g, 80%) as a colourless liquid.  $[\alpha]_{\text{D}}^{20} = +106.4$  (*c* 1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 0.93 (t, 3H, CH<sub>3</sub>), 1.53 (d, 3H, CH<sub>3</sub>), 1.66 (sextet, 2H, CH<sub>2</sub>), 2.29 (t, 2H, CH<sub>2</sub>), 3.81 (s, 3H, CH<sub>3</sub>), 5.88 (q, 1H, CH), 6.89 (d, 2H, Ph), 7.31 (d, 2H, Ph); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 14.0 (CH<sub>3</sub>), 18.8 (CH<sub>2</sub>), 22.4 (CH<sub>3</sub>), 36.9 (CH<sub>2</sub>), 55.6 (CH<sub>3</sub>), 72.1 (CH), 114.2 (CH), 127.9 (CH), 134.3 (C), 159.6 (C), 173.3 (C).

#### 4.7. (*R*)-1-Indanyl butyrate 5j

Purification by flash chromatography (hexane/EtOAc) afforded (*R*)-1-indanyl butyrate **5j** (1.21 g, 74%) as a colourless liquid.  $[\alpha]_{\text{D}}^{20} = +76.5$  (*c* 1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 0.96 (t, 3H, CH<sub>3</sub>), 1.67 (sextet, 2H, CH<sub>2</sub>), 2.12 (m, 1H, CH<sub>2</sub>), 2.31 (t, 2H, CH<sub>2</sub>), 2.53 (m, 1H, CH<sub>2</sub>), 2.92 (m, 1H, CH<sub>2</sub>), 3.10 (m, 1H, CH<sub>2</sub>), 6.24 (dd, 1H, CH), 7.26 (m, 3H, Ar), 7.42 (d, 1H, Ar); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 14.0 (CH<sub>3</sub>), 18.9 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 32.7 (CH<sub>2</sub>), 36.8 (CH<sub>2</sub>), 78.4 (CH), 125.2 (CH), 125.9 (CH), 127.1 (CH), 129.2 (CH), 141.6 (C), 144.7 (C), 174.1 (C).

#### 4.8. (*R*)-2-Octyl phenylacetate 6k

Purification by flash chromatography (hexane/EtOAc) afforded (*R*)-2-octyl phenylacetate **6k** (1.25 g, 63%) as a colourless liquid.  $[\alpha]_{\text{D}}^{20} = -12.5$  (*c* 1.04, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 0.88 (t, 3H, CH<sub>3</sub>), 1.22 (m, 11H, β-CH<sub>3</sub> + 4 × CH<sub>2</sub>), 1.59 (2 × m, 2H, diastereotopic, β-CH<sub>2</sub>), 3.60 (s, 2H, CH<sub>2</sub>), 4.92 (sextet, 1H, α-H), 7.30 (m, 5 H, Ph); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 14.4 (CH<sub>3</sub>), 20.3 (CH<sub>3</sub>), 22.9 (CH<sub>2</sub>), 25.6 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>), 36.3 (CH<sub>2</sub>), 42.2 (CH<sub>2</sub>), 71.9 (CH), 127.3 (CH), 128.9 (CH), 129.6 (CH), 134.8 (C), 171.6 (C).

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#### References

- (a) For a comprehensive survey of asymmetric hydrogenations of ketones, see: Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; VCH: New York, 2000; pp 34–83; (b) Specific to asymmetric hydrosilylations, see: Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; VCH: New York, 2000; pp 111–126; (c) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151.
- Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67–77.
- (a) Itsuno, S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 289–315; (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
- (a) Stampfer, W.; Kosjek, B.; Faber, K.; Kroutil, W. J. *Org. Chem.* **2003**, *68*, 402–406; (b) Stampfer, W.; Kosjek, B.; Moitzi, C.; Kroutil, W.; Faber, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1014–1017; (c) Nakamura, K.; Takenaka, K.; Fujii, M.; Ida, Y. *Tetrahedron Lett.* **2002**, *43*, 3629–3631.
- Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26.

6. (a) Bio-catalytic oxidations, see for example: Stampfer, W.; Kosjek, B.; Faber, K.; Kroutil, W. *Tetrahedron: Asymmetry* **2003**, *14*, 275–280; (b) Chemo-catalytic oxidations, see: Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumara, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 288–290.
7. Gais, H. J.; Theil, F. In *Enzyme Catalysis in Organic Synthesis (A comprehensive Handbook, Second, Completely Revised and Enlarged Edition)*; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, **2002**; Vol. II, pp 335–578.
8. (a) Stürmer, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 1173–1174; (b) Parker, R. J.; Williams, J. M. J. *Recent Res. Devel. Org. Bioorg. Chem.* **1999**, *3*, 47–64; (c) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321–331; (d) Faber, K. *Chemistry* **2001**, *7*, 5004–5010; (e) Kim, M.-J.; Yangsoo, A.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578–587; (f) Kim, M.-J.; Yangsoo, A.; Park, J. *Curr. Opin. Biotechnol.* **2003**, *14*, 131; (g) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327; (h) Pàmies, O.; Bäckvall, J.-E. *Curr. Opin. Biotechnol.* **2003**, *14*, 407–413; (i) Pàmies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247–3261; (j) Turner, N. J. *Curr. Opin. Chem. Biol.* **2004**, *8*, 114–119.
9. See Refs. 8e, 8f, 8i and 8h.
10. Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J. *Tetrahedron Lett.* **1996**, *37*, 7623–7626.
11. (a) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650; (b) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **1997**, *36*, 1211–1212; (c) Martín-Matute, B.; Edin, M.; Bogár, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535–6539; (d) Edin, M.; Steinreiber, J.; Bäckvall, J.-E. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5761–5766.
12. (a) Verzijl, G. K. M.; de Vries, J. G.; Broxterman, Q. B. *PCT Int. Appl.* **2001**, WO 2001090396 A1 20011129; (b) Verzijl, G. K. M.; Broxterman, Q. B. *PCT Int. Appl.* **2003**, WO 2003043575 A2 20030530; (c) Kim, M.-J.; Park, J. W.; Han, M.-Y.; Choi, M.-Y.; Choi, Y.-K.; Lee, J.-K. *PCT Int. Appl.* **2004**, WO 2004039998 A1 20040513; (d) Park, J. W.; Kim, M.-J.; Koh, J. H.; Jung, H. M. *PCT Int. Appl.* **2001**, WO 2001040157 A1 20010607; (e) Park, J. W.; Kim, M.-J.; Koh, J. H.; Jung, H. M. *PCT Int. Appl.* **2001**, WO 2001028971 A1 20010426; (f) Park, J. W.; Kim, M.-J.; Koh, J. H.; Jung, H. M. *PCT Int. Appl.* **2001**, WO 2001028970 A1 20010426; (g) Park, J. W.; Kim, M.-J.; Koh, J. H.; Jung, H. M. U.S. 6,753,443 B1, 2004.
13. Jung, M. H.; Koh, J. H.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 2487–2490.
14. Choi, J. A.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373.
15. Adkins, H.; Elofson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc.* **1949**, *71*, 3622–3629.
16. The addition of the ketone as a co-catalyst has already been considered. However it was concluded that it had no additional advantage. Under the given circumstances, the formation of the ketone (enhancing the racemisation) takes place by dehydrogenation of the substrate alcohol. See Ref. 11a.
17. Ghanem, A.; Schurig, V. *Chirality* **2001**, *13*(2), 118–123.
18. *Designing Safer Chemicals*; Garrett, R. L., De Vito, S. C., Eds.; American Chemical Society Symposium Series 640: Washington, DC, 1996; Chapter 1.
19. (a) Highlighting the uses and preparation of **4** in current research, see: Prabhakaran, R. *Synlett* **2004**, *11*, 2048–2049; (b) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885–3891; (c) Sappa, E.; Cetini, G.; Gambino, O.; Valle, M. J. *Organomet. Chem.* **1969**, *20*, 201–204; (d) Bruce, M. I.; Knight, I. R. *J. Organomet. Chem.* **1968**, *12*, 411–413.