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Impact of variation of the acyl group on the efficiency and selectivity of the lipase-mediated resolution of 2-phenylalkanols

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ABSTRACT

By tuning the steric properties of the acyl group to control the efficiency and selectivity of the resolution, 2-phenyl-1-propanol **1a** was prepared by lipase-catalysed hydrolysis using a short-chain acyl group, with *E*-values of up to 66 (*ee* up to 95%). 2-Phenylbutan-1-ol **1b** was similarly resolved (up to 86% *ee*) using the optimised conditions, while the ester of the more sterically demanding 3-methyl-2-phenylbutan-1-ol **1c** proved resistant to enzymatic hydrolysis under these conditions.

1. Introduction

The use of biocatalysts in organic synthesis is a growing and attractive method for achieving chemical transformations.[1] Enzymes, by their nature, have excellent chemo-, regio- and enantioselectivity, which if utilised correctly can give superior results to chemical catalysts.[2]

Hydrolases are the most studied biocatalysts and have found application in many industrial processes.[1] Lipases are ubiquitous enzymes belonging to the family of serine hydrolases and can be found in animals, plants, bacteria, and fungi.[3] Lipases naturally catalyse the reversible hydrolysis of the ester bonds in triacylglycerols, producing the free fatty acids, and are highly enantioselective in the kinetic resolution of carboxylic acids, alcohols, and related derivatives.[4] Lipases are the most frequently used enzymes in organic synthesis due in part to being inexpensive, commercially available, and stable, but also due to their wide substrate scope and high regio-, stereo-, and chemoselectivity. Another advantage is that lipases do not need cofactors. They are also very useful because they naturally act on the lipid water interface, thus increasing their substrate scope beyond water soluble compounds.

Amongst wild type enzymes, many different strategies can be employed to increase the selectivity of lipases including, but not limited to: the addition of organic solvents,[5–7] temperature variation,[8,9] immobilisation and modification of the enzyme,[10,11] the presences of additives,[12–14] and, in the case of (trans)esterification, modification of the acyl donor.[15–21]

Studies on the selectivity of lipases usually focus on compounds where the stereogenic centre is adjacent to the site of reaction, e.g. α-alkyl carboxylic acids or secondary alcohols. Secondary alcohols are so well studied that there are size-based rules for predicting the stereochemical outcome with well-known lipases (Fig. 1).[1] When the stereogenic centre is removed from the reaction site, e.g. β- or γ-alkyl carboxylic acids or primary alcohols, it can lead to challenges in terms of efficiency and selectivity. These systems are therefore less studied than their secondary alcohol counterparts.[22–26] While there are a few examples of predictive models for the stereochemical outcome with these types of compounds, they are very limited and only include very few lipases.[27] While the lipase-mediated resolution of primary alcohols is known, an efficient resolution of 2-phenyl-1-propanol **1a** has proven challenging.[28]

We have previously demonstrated the lipase mediated kinetic resolution of chiral 3-aryl alkanoic acids, showing that hydrolases can efficiently resolve compounds with remote stereocentres.[29,30] While early results from our group and others indicated that the resolution was feasible with R = Me only,[22] extensive tuning of the reaction conditions gave excellent enantioselectivities for both the chiral acid and ester substrate even with *R* substituents as large as *tert*-butyl (Fig. 2).

We wished to extend this work to focus on derivatives with the stereogenic centre on the alcohol moiety, again remote from the reacting site. Specifically, we wanted to exploit the excellent chemo-, regio- and enantioselectivity associated with lipases in

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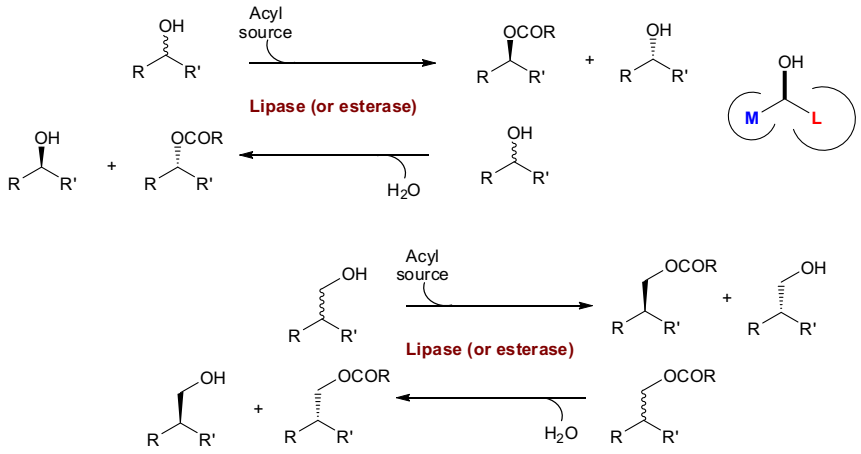


Figure 1. Hydrolysis and transesterification of chiral secondary and primary alcohols.

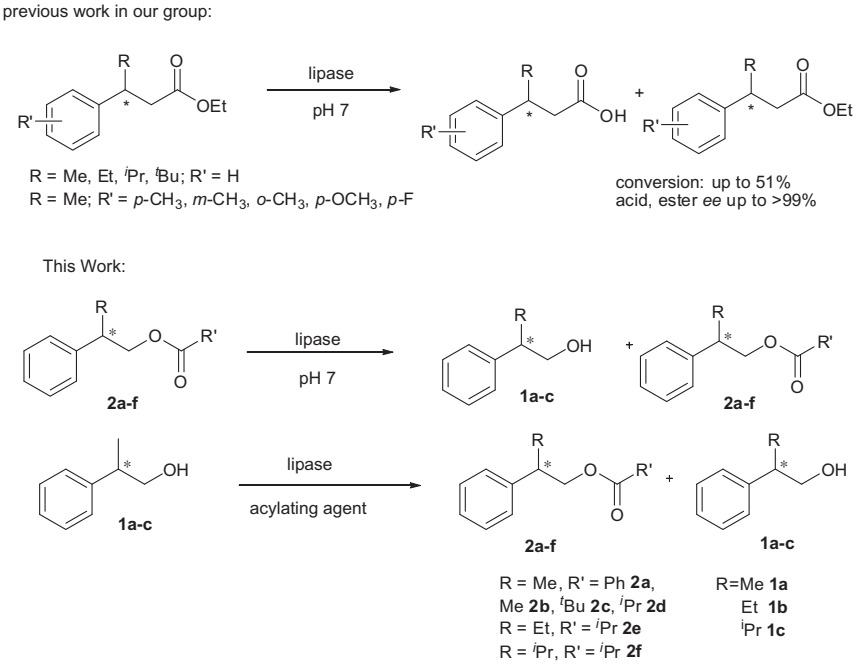


Figure 2. Previous work in our group.

the synthesis of 2-phenyl-1-propanol **1a**, studying both the transesterification and hydrolysis reactions of 2-phenyl-1-propanol **1a**, and derivative esters **2a**–**d**, respectively (Fig. 2). Chiral primary alcohols, with a benzylic stereocentre, can be used in the synthesis of 2-arylpropionic acids, a common class of nonsteroidal anti-inflammatory drugs (NSAIDs),[31,32] as well as in the synthesis of fragrance molecules.[33,34]

There have been several reports of the resolution of racemic primary alcohols using alcohol dehydrogenases, where the mixture is racemised on oxidation, and resolved on reduction.[35,36] However, while this is a dynamic kinetic resolution, a disadvantage is that a cofactor is required. 2-Phenyl-1-propanol **1a** has previously been synthesised enantioselectively by asymmetric methylation of styrene oxide, followed by a lipase catalysed transesterification to further enhance the *ee*.[37]

Transesterification of 2-phenyl-1-propanol **1a** has also been extensively studied, by variation of the vinyl ester used to investigate resolution (Fig. 3).[19,28,38–41] Usually, the ester groups are long chains with substituted terminal phenyl groups. In the case of the hydrolytic reaction, these larger ester groups are not atom economical, and can cause problems in purification, thus restricting synthetic utility. The impact of variation of the acylating agent has been studied, including the effect of a phenyl group on the

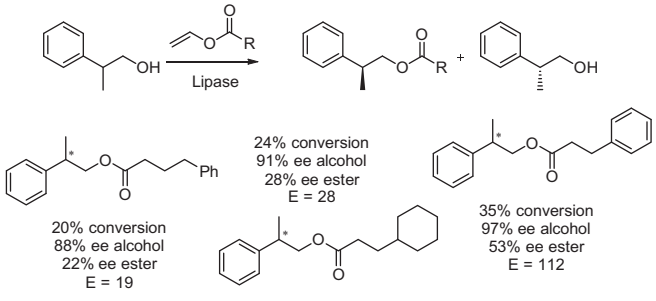


Figure 3. Product esters from the transesterification of 2-phenyl-1-propanol **1a** using long chain acyl donors.

resolution (a phenyl group at β-position is favourable),[19] the length of the alkyl chains (longer chains tend to give better selectivity),[15,42] and the electronic effects of the acyl chain (with isomeric pentenoic acids as acyl donors it was shown that the position of the double bond is important).[15]

Enantioenriched 2-aryl propanols resolved using lipases have been used in the synthesis of sesquiterpenes[28] and fragrance molecules.[33,34]

The resolution of 2-phenylpropyl benzoate **2a** by enzymatic hydrolysis with just four lipases has previously been reported.[18] Conversion of up to 39% was achieved with the highest *ee* for the alcohol being 88%.

Investigations into the impact of smaller acyl groups, aside from acetate,[28] are uncommon, with very few reports in the resolution of 2-phenyl-1-propanol **1a** and with poor selectivity ($E < 10$).[25,43,44] Herein we examined lipase mediated resolution with small acyl groups as a means to resolve 2-phenyl-1-propanol **1a**, which are more atom economical than use of larger acyl groups, and hold a clear advantage in product isolation, as the acid by-product can be removed in aqueous work up.

The preparation of derivatives of 2-phenyl-1-propanol **1a** with larger alkyl substituents **1b** and **1c** by lipase catalysed reaction has rarely been investigated. 2-Phenyl-1-butanol **1b** has previously been prepared by hydrolysis of the corresponding acetate, with poor *E*-value ($E = 2$).[25] There are a few reports of the transesterification of 2-phenyl-1-butanol **1b** with *ee* values of up to 69% for the alcohol **1b**.[19,45–48] *E*-Values of up to 142 have been achieved, however, these resolutions require the use of acyl donors with large acyl groups.[19] 3-Methyl-2-phenyl-1-butanol **1c** resolution by lipase-catalysed transesterification has been reported, usually with much longer reaction times than for **1b**, and with *ee* values of up to 74% for the alcohol.[45–47]

2. Results and discussion

The esters **2a–f** were prepared from the corresponding alcohols and acid chlorides using literature methods[49] as shown in Scheme 1, where **2a** and **2b** are previously reported compounds,[49,50] and **2c–f** are novel compounds. Alcohols **1a** and **1b** are commercially available, while **1c** was prepared by literature methods.[51]

The resolution was first attempted using hydrolytic reactions with 2-phenylpropyl benzoate **2a** as substrate, which was screened using a targeted panel of lipases,[52] as previous studies were limited to only a few lipases.[18] Of the 52 enzymes tested, 15 gave no conversion, 22 gave conversion under 10%, while 4 gave 100% conversion with no selectivity. A selection of the results are shown below (Table 1). The lipase from *Pseudomonas cepacia* (Table 1, entry 4) furnished the product alcohol with excellent enantioselectivity, which surpassed previously reported results ($E = 42$, cf. 28 highest to date).[18] The lipase from *Candida cylindracea* (Table 1, entry 15) resulted in good conversion but without selectivity. The use of this lipase was subjected to a limited solvent screen, including 1-octanol (Table 1, entry 16), which furnished $ee_s = 27\%$, $ee_p = 20\%$, $c = 42\%$. While this is poorly selective overall, it shows a significant increase in selectivity compared to the outcome in the absence of the organic cosolvent. The resolution was also attempted using the transesterification reaction, since the selectivity can be changed by changing the mode of reaction.[48] The transesterification reaction with vinyl benzoate gave either no conversion or full conversion, depending on the lipase used. The results can be found in the ESI.

Herein, some loss of 2-phenyl-1-propanol **1a** was observed on prolonged evaporation of the solvents. Accordingly, E_{calc} [$E_{calc} = ee_s/(ee_s + ee_p)$] is a more reliable indicator of the extent of conversion than the ^{1}H NMR in this instance.

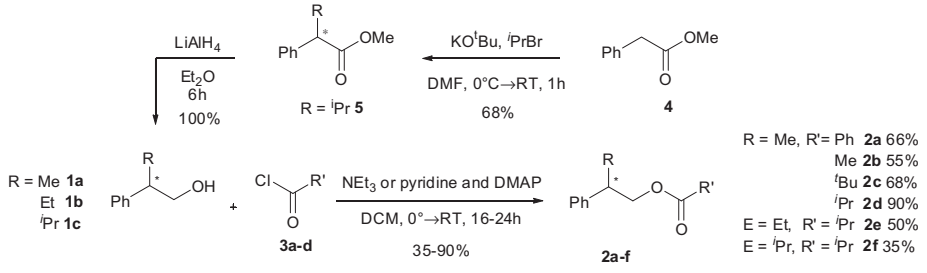
In order to achieve high enantioselectivity with good conversion, alternative ester groups were employed; firstly, it was decided to test the commercial enzymes against 2-phenylpropyl acetate **2b**. Resolution by hydrolysis has previously been reported but is poorly selective ($E = 4$) for 2-phenylpropyl acetate **2b**.[54] More common however, is the resolution of the acetate **2b** by transesterification, again with limited enantioselectivity under standard conditions.[28,40,45,46]

The resolution of 2-phenyl-1-propanol **1a** was attempted using a smaller acyl group, acetate **2b**. Before carrying out the transesterification reactions, the effect of molecular sieves was investigated (data in ESI). The presence or absence of molecular sieves had little effect on the transesterification reactions with vinyl acetate, with molecular sieves increasing the conversion, but having very little effect on the *E* value, which is consistent with previously reported findings.[22] The resolution of **1a** was attempted using both transesterification and hydrolysis (Table 2) reactions. The transesterification reactions were carried out in the absence of a lipase, as a control, which showed no chemical acylation over 24 h despite the high loading of vinyl acetate. Similarly, it was demonstrated that hydrolysis did not occur without a lipase in the hydrolytic reactions.

The extent of acylation is very sensitive to reaction time, with reactions proceeding essentially to completion at longer reaction times with some lipases. By careful control of the reaction time, the extent of the transformation was optimised to ~50%, although with modest enantioselectivity in each case. The five lipases tested gave >50% hydrolysis product after 65 h, showing that the reaction was time sensitive. The times were reduced but the resolutions were not selective enough when the acetate **2b** was the substrate. This is not unexpected, as acetate **2b** provides limited selectivity at 30 °C, however, this screen provided an important reference point.[18,28,40,45,54,55]

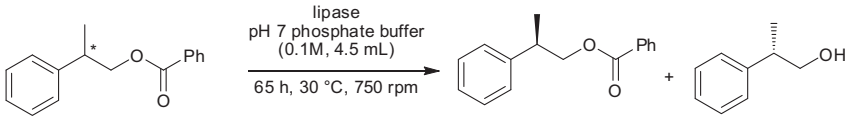
In the context of the high selectivity but poor conversion using the pivalate ester **2c** and the fast reaction but poor selectivity using the acetate ester **2b**, isobutyrate ester **2d** was next explored.

In order to explore the impact of a more sterically demanding ester, the pivaloyl ester, 2-phenylpropyl pivalate **2c**, was prepared



Scheme 1. Preparation of ester substrates **2a–f**.

Table 1
Hydrolysis of 2-phenylpropyl benzoate **2a**

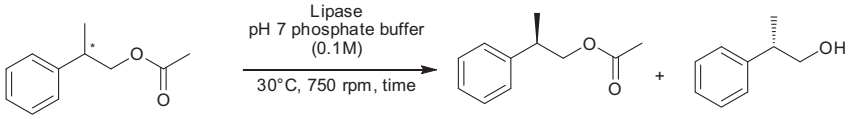


rac-**2a** (*R*)-**2a** (*S*)-**1a**

Entry	Lipase	Conversion (%)		*ee*[a] (%)		E^{53}
		NMR	E_{calc}	ee_s	ee_p	
1	Lipase A from *Burkholderia cepacia*	47	48	66	71 (*S*)	11
2	Lipase E from *Alcaligenes sp*	30	33	23	46 (*S*)	3.4
3	Lipase from *Pseudomonas fluorescens*	29	29	28	69 (*S*)	7.1
4	Lipase from *Pseudomonas cepacia*	23	32	44	93 (*S*)	42
5	Lipase from *Aspergillus niger*	22	24	8	26 (*S*)	1.8
6	Porcine *pancreas* type II	17	19	7	30 (*S*)	2.0
7	Lipase C from *Alcaligenes* sp.	15	32	18	39 (*S*)	2.7
8	*Candida antarctica* lipase B (immobilised)	15	19	21	87 (*S*)	17
9	Lipase D from *Alcaligenes* sp.	14	11	8	64 (*S*)	4.9
10	Lipase F from *Alcaligenes* sp.	11	7	4	57 (*S*)	3.8
11	Lipase from *Candida antarctica*	10	18	20	89 (*S*)	20
12	Hog Pancreas Lipase	4	—[b]	—[c]	—[c]	—[b]
13	*Pseudomonas fluorescens* (immobilised)	2	—[b]	—[c]	—[c]	—[b]
14	Amano PS Lipase	9	—[b]	—[c]	—[c]	—[b]
15	Lipase from *Candida cylindracea*	48	—[d]	0	0	—[d]
16	Lipase from *Candida cylindracea* with 17% v/v 1-octanol	—[e]	42	27	20 (*R*)	1.9

[a] Enantiomeric excess values determined by chiral HPLC analysis using Chiralcel OBH, 1 ml/min, 1:99 2-propanol/hexane, except for entries 3–6, 8 and 11 which were determined using Cell 2, 0.6 ml/min, 3:97 2-propanol/hexane, to separate the alcohol and Chiralcel ODH, 0.25 mL/min, 1:99 2-propanol/hexane for the ester.
[b] E_{calc} and E values were not determined, as enantioselectivity values were not measured when conversion <10%.
[c] Conversion was not determined when conversion was <10%.
[d] E_{calc} and E values were not determined, as enantioselectivity values were <1%.
[e] Conversion was not measured by NMR, only E_{calc} conversion was determined due to the presence of 1-octanol.

Table 2
Hydrolysis of 2-phenypropylacetate **2b**, showing the initial screen (t = 65 h) and the optimised times ($c \approx 50\%$)



rac-**2b** (*R*)-**2b** (*S*)-**1a**

Entry	Lipase Source	Time (h)	Conversion (%)		*ee*[a] (%)		E^{53}
			NMR	E_{calc}	ee_s	ee_p	
1a	Hog pancreas Lipase	65	61	55	65	54 (*S*)	6.4
b		48	56	56	71	55 (*S*)	7.1
2a	*Candida antarctica* Lipase B (immobilised)	65	87	62	26	16 (*S*)	1.7
b		24	55	54	72	61 (*S*)	8.7
c		18	56	57	73	55 (*S*)	7.3
3a	*Pseudomonas fluorescens* (immobilised)	65	82	62	10	16 (*S*)	1.5
b		24	52	53	17	15 (*S*)	1.6
4a	Amano PS Lipase	65	100	—[b]	—[3]	—[b]	—[b]
b		6	57	57	25	19 (*S*)	1.8
5a	Lipase from *Candida cylindracea*	65	87	60	3	2 (*R*)	1.1
b		48	57	47	4	3 (*R*)	1.1
c		6	42	38	3	5 (*R*)	1.1

In the absence of an enzyme, the reaction gave no product after 65 h.
[a] Enantiomeric excess values were determined by chiral HPLC analysis using Chiralcel OBH, 0.5 ml/min, 1:99 2-propanol/hexane.
[b] Enantiomeric excess values were not measured as $c \approx 100\%$, E_{calc} and E values were not determined.

and screened for hydrolysis and transesterification. A selection of five lipases were tested under hydrolytic conditions but most showed poor conversion or selectivity (E = 1), these are included in ESI for reference. However, excellent selectivity was achieved in the hydrolytic reactions catalysed by Amano PS Lipase, albeit coupled with poor conversion (Table 3, entry 1). Increasing the reaction temperature to 50 °C, which is the optimum temperature for this lipase, and adding an organic cosolvent, increased the selectivity. This was accompanied by a decrease in conversion.

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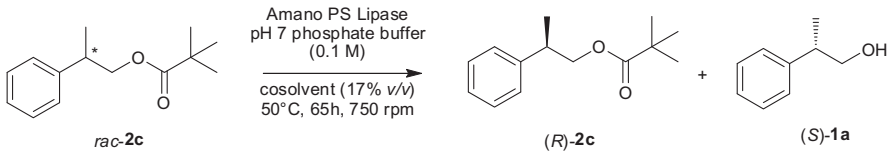
Table 3
Hydrolysis of 2-phenylpropyl pivalate **2c** using Amano PS Lipase in conjunction with organic cosolvents



rac-**2c** (*R*)-**2c** (*S*)-**1a**

Entry	Co solvent	Conversion (%)		*ee*[a] (%)		*E*[53]
		NMR	E_{calc}	ee_s	ee_p	
1a	—[b]	15	13	14	90 (*S*)	22
b	—	21	19	20	88 (*S*)	20
2	Methyl *tert*-Butyl Ether	<1	—[c]	0	81 (*S*)	—[c]
3	2-Propanol	—[d]	4	4	91 (*S*)	22
4	*n*-Heptane	<1	—[c]	0	>99 (*S*)	—[c]
5	Acetonitrile	2	—[c]	0	>99 (*S*)	—[c]

Initial reactions were carried out at 30 °C using the following enzymes, which gave conversion <10%: Hog pancreas lipase, Lipase from *Candida cylindracea*. The following enzymes gave no conversion: *Pseudomonas fluorescens* (immobilised), *Candida antarctica* lipase B (immobilised).
[a] Enantiomeric excess values were determined by chiral HPLC analysis using Chiralcel OBH, 0.5 ml/min, 1:99 2-propanol/hexane.
[b] Carried out at 30 °C, all other reactions are 50 °C.
[c] E_{calc} conversion and *E* were not determined as this requires *ee* >1.
[d] Conversion by NMR could not be determined because of the presence of the solvent peak.

In contrast, the transesterification reactions were poorly selective, with $E < 10$ for the lipases tested. Conversions of up to 33% were obtained but coupled with poor *ee* values for alcohol **1a** (up to 31%), with a moderate *ee* value for the ester (62%) (results not shown).

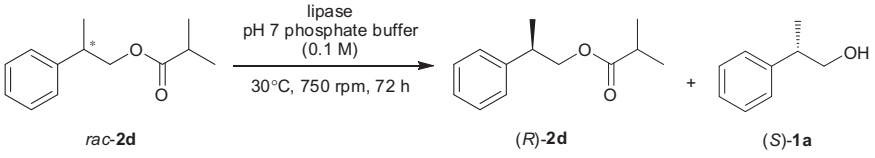
In the initial screening reactions, *Candida antarctica* Lipase B (immobilised) (Table 4, entry 2) showed very promising enantioselectivity for both the isobutyrate ester **2d** and the product alcohol **1a**. As a result, this transformation was subjected to an organic solvent screen (Table 5). The solvents tested provided the alcohol **1a** with up to 95% *ee*. *E*-values of up to 66 were achieved, with up to 95% *ee*. While a recent publication has suggested that less polar solvents have a positive effect on the performance of *Candida antarctica* Lipase B, in this instance no clear correlation was observed.[56]

Following this successful optimisation, the resolution of 2-phenyl-1-propanol **1a** was carried out on a preparative scale. The solvent chosen for scale up was *tert*-butanol on the basis of both efficiency and selectivity (Table 5, Entry 10) furnishing 2-phenyl-1-propanol **1a** in 34% isolated yield and the ester **2d** in 54% yield, after column chromatography, accompanied by *ee* values of 70% and 90%, respectively (Scheme 2). The isobutyric acid by-product was removed in the aqueous work up, and was not detected in the crude ^{1}H NMR of the reaction mixture, which is a clear advantage.

In order to ascertain if the reaction was a true resolution, the screen was repeated under the same conditions as the preparative scale resolution, for 24, 72 and 120 h, except that the lipase concentration was doubled. These reactions attained 56% conversion after 24 h, showing that the reaction was finished faster. However, the reaction continued past 50% conversion. The calculated conversions (E_{calc}) were as follows: 56%, 77%, 80% for 24 h, 72 h and 120 h respectively. In this case, the ester *ee* was excellent, 97–99% as expected for conversion over 50%, with the alcohol *ee* decreasing with increasing conversion (Table 6). This serves to show us that ester **2d** can be prepared with excellent enantioselectivity, when using a greater concentration of enzyme, in a much shorter time. However, the higher concentration of the lipase combined with a shorter time is unsuitable for the preparation of the enantiopure alcohol **1a** as the enantioselectivity is less than the previous results (Scheme 2).

Overall, these results indicate that by careful control of the reaction conditions and acyl group, the lipase-mediated hydrolysis can lead efficiently to highly enantioenriched 2-phenyl-1-propanol **1a** and 2-phenylpropyl isobuyrate **2d** in a synthetically useful process. The key to this was choosing the isobutyrate group as a

Table 4
Hydrolysis of 2-phenylpropyl isobutyrate **2d**



rac-**2d** (*R*)-**2d** (*S*)-**1a**

Entry	Enzyme source	Conversion (%)		*ee*[a] (%)		*E*[53]
		NMR	E_{calc}	ee_s	ee_p	
1	Hog pancreas lipase	17	15	11	60 (*S*)	4.5
2	*Candida antarctica* lipase B (immobilised)	46	46	76	90 (*S*)	44
3	Pseudomonas fluorescens (immobilised)	9	7	4	51 (*S*)	3.2
4	Amano PS lipase	64	67	81	40 (*S*)	5.4

Reaction carried out with no enzyme present resulted in no conversion. Reaction carried out with lipase from *Candida cylindracea* resulted in 100% conversion.
[a] Enantiomeric excess values were determined by chiral HPLC analysis using Chiralcel OBH, 0.5 ml/min, 1:99 2-propanol/hexane.

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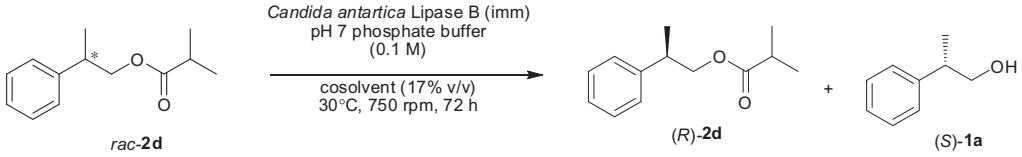
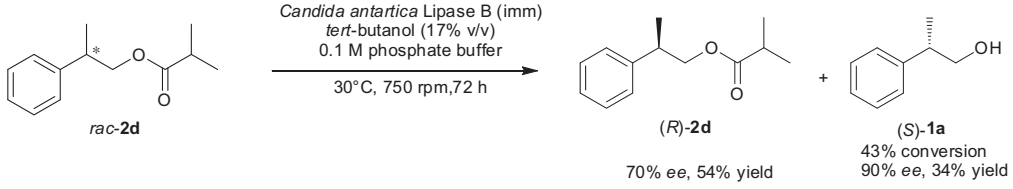
Table 5
Hydrolysis of 2-phenylpropyl isobutyrate **2d** by *Candida antarctica* lipase B (immobilised) in the presence of organic cosolvents



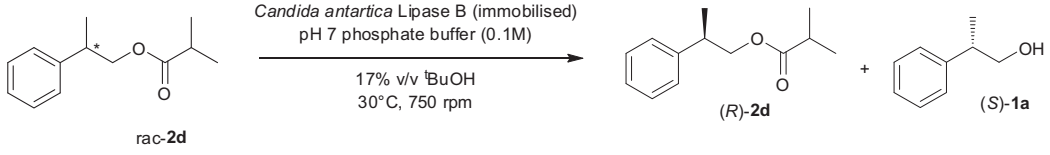
Entry	Co solvent	Conversion[a] (%)	*ee*[b] (%)		*E*[53]
			ee_s (*R*)	ee_p (*S*)	
1	–	46	76	90 (*S*)	44
2	1-Octanol	2	2	89 (*S*)	17
3	2-Propanol	21	24	93 (*S*)	33
4	Acetone[c]	33	47	95 (*S*)	60
5	Acetonitrile[c]	33	47	95 (*S*)	63
6	*n*-Heptane[c]	14	15	92 (*S*)	29
7	Methyl *tert*-butyl ether[c]	34	48	94 (*S*)	53
8	Hexane[c]	10	10	92 (*S*)	27
9	Diisopropyl ether	8	8	92 (*S*)	26
10	*t*-Butanol	48	85	91 (*S*)	59
11	2-Methyltetrahydrofuran[c]	14	15	95 (*S*)	41
12	Toluene	41	62	87 (*S*)	28
13	Cyclohexane	33	46	95 (*S*)	66
14	Pentane[c]	12	12	93 (*S*)	29

[a] E_{calc} conversion.
[b] Enantiomeric excess values were determined by chiral HPLC analysis using Chiralcel OBH 0.5 ml/min, 1:99 2-propanol/hexane.
[c] HPLC grade solvent used.



Scheme 2. Preparative scale synthesis of (*S*)-2-phenyl-1-propanol (*S*)-**1a** and (*R*)-2-phenylpropyl isobutyrate (*R*)-**2d**.

Table 6
Hydrolysis of 2-phenylpropyl isobutyrate **2d**



Entry	Time (h)	Conversion		*ee*[a] (%)		*E*[53]
		NMR	E_{calc}	ee_s	ee_p	
1	120	77	80	97	25 (*S*)	5.7
2	72	89	77	>99	29 (*S*)	7.6
3	24	64	56	>99	78 (*S*)	40

Shaking at 30 °C with no enzyme for 120 h gave conversion <1%.
[a] Enantiomeric excess values were determined by chiral HPLC analysis using Chiralcel OBH 0.5 ml/min, 1:99 2-propanol/hexane.

compromise between the pivaloyl (highly selective, poorly efficient) and the methyl (poorly selective and highly effective) groups (Fig. 4).

Encouraged by the excellent results using ester **2d**, esters **2e** and **2f** were subjected to hydrolysis using the optimised conditions for ester **2d** [*Candida antarctica* lipase B (immobilised), 72 h, 750 rpm]. The results for **2e** are shown in Table 7. Ester **2e** showed encouraging results for the initial screen using *Candida antarctica* lipase B (immobilised) (Entry 1) and was subjected to a small solvent screen, using the solvents which gave the highest E-values for hydrolysis of **2d**. Acetonitrile (Entry 4) showed the highest product

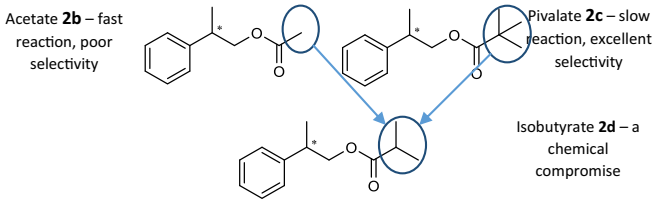
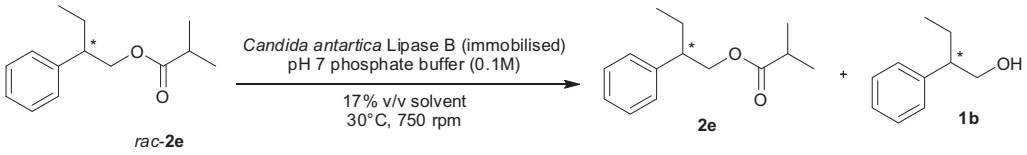


Figure 4. 2-phenylpropyl isobutyrate **2d**: a compromise between ester groups.

Table 7
Hydrolysis of 2-phenylbutyl isobutyrate **2e**



rac-**2e** **2e** **1b**

Entry	Solvent	Conversion[a] (%)	*ee*[b] (%)		*E*[53]
			ee_s	ee_p	
1	—	47	66	74	13
2	*tert*-Butanol	33	37	74	9.6
3	Acetone[c]	21	21	77	9.2
4	Acetonitrile[c]	24	28	86	17
5	Methyl *tert*-Butyl ether[c]	19	19	82	12
6	Cyclohexane	18	17	82	12

[a] E_{calc} conversion.
[b] Enantiomeric excess values were determined by chiral HPLC analysis using Chiralcel OJH 0.5 ml/min, 2:98 2-propanol/hexane.
[c] HPLC grade solvent used.

enantioselectivity, which was similar to the result for **2d**. Previously, the highest reported *ee* of **1b** by lipase-catalysed transesterification was 69% *ee*.[48] The more sterically demanding ester **2f** was not hydrolysed either in neat buffer or with *tert*-butanol (17% v/v).

3. Conclusion

2-Phenyl-1-propanol **1a** was resolved with excellent selectivity with up to 95% *ee* and up to 48% conversion, using a commercially available lipase and a small alkyl ester group, making the transformation selective and atom economical. *E* values of up to 63 were obtained. A preparative scale resolution was also performed, giving 43% conversion after 72 h, coupled with 34% yield of alcohol **1a** with 90% *ee* and 54% yield of ester **2d**, with 70% *ee*. Increasing the steric demand of the alkyl substituent at the remote stereocentre to ethyl **2e** gave similar enantioselectivity, while the use of the larger *iso*-propyl group **2f** led to no hydrolysis. This represents a substantial improvement on the previous reports using short acyl chains ($E < 10$). Key to this work was the systematic variation of the steric demand on both the acid and alcohol components of the ester to optimise the outcome in terms of both selectivity and efficiency.

4. Experimental

4.1. General

Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorus pentoxide, ethyl acetate was distilled from potassium carbonate. Hexane was distilled prior to use. Molecular sieves were activated by heating at 150 °C overnight. Organic phases were dried over anhydrous magnesium sulfate. Infrared spectra were recorded neat using a Perkin Elmer FTIR UATR2 spectrometer. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer, and all spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$), unless otherwise stated, using tetramethylsilane (TMS) as an internal standard and chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) and coupling constants are expressed in Hertz (Hz). Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer in electrospray ionisation (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer in electrospray ionisation mode (ESI) using 50% water/acetonitrile containing 0.1% formic acid as eluent. Wet flash chromatography was performed using Kieselgel Silica Gel 60, 0.040–0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV (254 nm) light detection and $KMnO_4$ staining. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 589 nm in a 1 cm cell; concentrations (*c*) are expressed in g/100 mL. $[\alpha]_D^{20}$ is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}. Hydrolases were from Almac Sciences except Amano PS Lipase, *Candida antarctica* lipase B (immobilised on ImmoBead 150), Hog pancreas lipase, *Pseudomonas fluorescens* (immobilised on Sol–gel), and Lipase from *Candida cylindracea* which were purchased from Sigma-Aldrich chemical company. All enzymatic reactions were performed on a VWR Incubating Mini Shaker 4450. All reagents are analytical grade and purchased from Sigma-Aldrich chemical company, except 2-phenyl-1-propanol **1a** which was purchased from TCI. Enantiomeric excess values were measured by high performance liquid chromatography (HPLC) using a Chiralcel® OB-H column (5 × 250 mm), Chiralcel® OD-H column (5 × 250 mm) and Chiralcel® OJ-H column (5 × 250 mm) purchased from Daicel Chemical Industries, Japan and Phenomenex Cellulose 2 column (5 × 250 mm), purchased from Phenomenex Inc., UK. Mobile phase and flow rate are included where appropriate, and the detector wavelength was 209.5 nm with a column temperature set at 25 °C. HPLC analysis was performed on a Waters alliance 2690 separations module with a PDA detector. When only a single enantiomer was detected, the enantiomeric excess is quoted as >99%.

4.2. Lipase-catalysed hydrolysis reactions

In a typical experiment, 8 mg of powdered lipase, or 18 mg of immobilised lipase, were added to the ester substrate **2a–f** (50 mg) in 0.1 M phosphate buffer at pH 7 (4.5 mL). Cosolvents (HPLC grade, obtained from Sigma Aldrich) were added (0.77 mL, 17% v/v) as indicated. The small test tubes were sealed and agitated at 750 rpm at 30 °C for 65 h, unless otherwise stated. The aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic extracts were filtered through Celite® and concentrated under reduced pressure. The conversion was determined by ^{1}H NMR; the sample was reconcentrated and dissolved in 10:90 2-propanol/hexane (HPLC grade) and enantioselectivity was determined by chiral HPLC analysis.

4.3. Lipase-catalysed transesterification reactions

In a typical experiment, 8 mg of powdered lipase, or 18 mg of immobilised lipase, were added to the substrate **1a** (10 mg) in vinyl acetate (0.5 mL), with crushed 4 Å molecular sieves, as indicated. A solvent (HPLC grade, Sigma Aldrich) was added if required and the test tubes were sealed and agitated at 150 rpm for at 30 °C for the times specified in the relevant tables. The reaction mixture was diluted with ether (~5–10 mL), filtered through Celite® and concentrated under reduced pressure. The conversion was determined by ^{1}H NMR; the sample was reconcentrated and dissolved in 10:90 2-propanol/hexane (HPLC grade) to a concentration of ~1 mg/mL and enantioselectivity was determined by chiral HPLC analysis as indicated.

4.4. 2-Phenylpropyl benzoate 2a[50]

Benzoyl chloride **3a** (3.96 g, 28.2 mmol) in DCM (20 mL) was added slowly to a stirring solution of 2-phenyl-1-propanol **1a** (4.0 mL, 29.2 mmol) and triethylamine (4.67 mL, 33.6 mmol) in DCM (20 mL) at 0 °C. The ice bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM (90 mL). The solution was washed with water (2 × 100 mL), aqueous HCl (10%, 2 × 100 mL), brine (150 mL), dried, filtered and concentrated to give the crude product as a pale yellow oil. The product was purified by column chromatography on silica gel using hexane/ethyl acetate (95:5) as eluent, giving pure ester **2a** (4.434 g, 66%) as a colourless oil. IR (neat): 2969 (C—H), 1716 (C=O), 1268, 1110 (C—O), 698 (C—H Ar) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–8.04 [m, 2H, Ar-*H*], 7.49–7.57 [m, 1H, Ar-*H*], 7.19–7.46 [m, 7H, Ar-*H*], 4.33–4.48 [sym m, 2H, C(1)H_2], 3.17–3.33 [sym m, 1H, C(2)*H*], 1.40 [d, *J* = 7.0 Hz, 3H, C(2)CH_3] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.5 [*C*=O], 143.2 [4° Aromatic *C*], 132.9 [Aromatic *C*H], 130.4 [4° Aromatic *C*], 129.6, 128.5, 128.3, 127.4, 126.7, [5 × Aromatic *C*H], 69.9 [CH_2O], 39.1 [CH], 18.1 [CH_3] ppm. HRMS (ES+): *m*/*z* calcd for [$C_{16}H_{17}O_2$]$^+$ 241.1223; found: 241.1229. HPLC: Chiralcel OBH, 1:99 (2-propanol/hexane), 1 ml/min. RT = 10.0 min (*R*)-**2a**, 12.4 min (*S*)-**2a** All data are in agreement with previously reported data except signal for C(1)H_2 which is reported as a doublet, and the signal here is a symmetrical multiplet.

4.5. 2-Phenylpropyl acetate 2b[49]

Anhydrous pyridine (2.7 mL, 2.61 g, 33.04 mmol, 1.5 equiv) and acetyl chloride **3b** (1.567 mL, 1.73 g, 22.0 mmol, 1.0 equiv) were added to a stirring solution of 2-phenyl-1-propanol **1a** (3.0 g, 22.0 mmol, 1.0 equiv) and DMAP (134 mg, 1.1 mmol, 5 mol %) in DCM (75 mL) at 0 °C. The solution was removed from the ice bath and stirred for 24 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (40 mL) and was stirred until no more gas was evolved (approx. 40 min). The layers were separated and the organic layer was washed with satd aq $CuSO_4$ (3 × 40 mL). The combined aqueous layers were extracted with DCM (50 mL). The organic layers were combined and washed with water (2 × 100 mL), satd aq $NaHCO_3$ (100 mL), brine (100 mL), dried, filtered and concentrated to give the crude product as a colourless oil. Purification by column chromatography on silica gel using hexane/ethyl acetate (95:5) as eluent gave pure ester **2b** (2.16 g, 55%) as a colourless oil. IR (neat): 2968 (C—H), 1737 (C=O), 1373, 1227 (C—O), 699 (C—H Ar) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11–7.41 [m, 5H, Ar-*H*], 4.05–4.27 [sym m, 2H, CH_2O], 3.00–3.19 [sym m, 1H, *C*HCH$_3$], 2.00 [s, 3H, COCH_3], 1.30 [d, *J* = 7.1 Hz, 3H, CHCH_3] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.0 [*C*=O], 143.2 [4° Aromatic *C*], 128.5, 127.3, 126.7 [3 × Aromatic *C*H], 69.4 [CH_2], 38.9 [*C*(2)H], 20.9 [COCH_3], 18.1 [CH_3] ppm. HPLC: Chiralcel OBH, 0.5:99.5 (2-propanol/hexane), 0.5 ml/min. RT = 30.1 min (*S*)-**2b**, 34.5 min (*R*)-**2b**.

4.6. 2-Phenylpropyl pivalate 2c

Prepared following the procedure for **2b** using anhydrous pyridine (2.7 mL, 2.61 g, 33.04 mmol, 1.5 equiv), pivaloyl chloride **3***C* (2.7 mL, 22.0 mmol, 1.0 equiv), 2-phenyl-1-propanol **1a** (3.04 g, 22.0 mmol, 1.0 equiv) and DMAP (134 mg, 1.1 mmol, 5 mol %) in DCM (75 mL) to give the crude product as a colourless oil. Purification by column chromatography on silica gel using hexane/ethyl acetate (95:5) as eluent gave pure ester **2c** (3.273 g, 68%) as a colourless oil. IR (neat): 2971 (C—H), 1727 (C=O), 1282, 1150 (C—O), 699 (C—H) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.37 [m, 5H, Ar-*H*], 4.15 [dq, *J* = 10.8 Hz, *J* = 6.9 Hz, 2H, C(1)H_2], 3.02–3.29 [sym m, 1H, C(2)*H*], 1.31 [d, *J* = 6.9 Hz, 3H, C(3)H_3], 1.13 [9H, s, C(CH_3)$_3$]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.9 [*C*(3)H$_3$], 26.1 [C(*C*H$_3$)$_3$], 37.7 [*C*(CH$_3$)$_3$], 38.0 [*C*(2)H], 68.2 [*C*H$_2$O], 125.6, 126.3, 127.4 [3× Aromatic *C*H], 142.3 [4° Aromatic *C*], 177.3 [*C*=O] ppm. HRMS (ES+): calcd for [$C_{14}H_{21}O_2$]$^+$: 221.1542; found: 221.1541. HPLC: Chiralcel OBH, 1:99 (2-propanol/hexane), 0.5 ml/min. RT = 9.5 min (*S*)-**2c**, 13.1 min (*R*)-**2c**. This compound is novel and has been fully characterised.

4.7. 2-Phenylpropyl isobutyrate 2d

Prepared following the procedure for **2b** using anhydrous pyridine (1.05 mL, 0.98 g, 15 mmol, 1.5 equiv), isobutyryl chloride **3d** (1.2 mL, 10 mmol, 1.0 equiv), 2-phenyl-1-propanol **1a** (1.4 mL, 10 mmol, 1.0 equiv) and DMAP (61 mg, 0.5 mmol, 5 mol %) in DCM (35 mL) to give the crude product as a colourless oil. Purification by column chromatography on silica gel using hexane/ethyl acetate (90:10) as eluent gave pure ester **2d** (1.862 g, 90%) as a colourless oil. IR (neat): 2972 (C—H), 1732 (C=O), 1190, 1153 (C—O), 699 (C—H Ar) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 [d, *J* = 7.0 Hz, 3H, CH(CH_3)$_2$], 1.11 [d, *J* = 7.0 Hz, 3H, CH(CH_3)$_2$], 1.31 [d, *J* = 7.0 Hz, 3H, CH$_2$CH_3], 2.50 [sept, *J* = 7.0 Hz, 1H, *C*H(CH$_3$)$_2$], 3.00–3.22 [sym m, 1H, *C*HCH$_2$O], 4.00–4.32 [sym m, 2H, C(1)H_2], 7.10–7.43 [m, 5H, Ar-*H*]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.0 [*C*(4)H$_3$], 18.9 [CH(*C*H$_3$)$_2$], 34.0 [*C*H(CH$_3$)$_2$], 39.0 [*C*(3)H], 69.1 [*C*H$_2$O], 126.6, 127.3, 128.4 [3 × Aromatic *C*H], 143.3 [4° Aromatic *C*], 177.0 [*C*=O] ppm. HRMS (ES+) calcd for [$C_{13}H_{19}O_2$]$^+$: 207.1380; found: 207.1381. HPLC: Chiralcel OBH, 1:99 (2-propanol/hexane), 1 ml/min. RT = 6.6 min (*R*)-**2d**, 11.1 min (*S*)-**2d**. This compound is novel and has been fully characterised.

4.8. 2-Phenylbutyl isobutyrate 2e

Prepared following the procedure for **2b** using anhydrous pyridine (0.49 mL, 0.48 g, 6.1 mmol, 1.5 equiv), isobutyryl chloride **3d** (0.42 mL, 4.0 mmol, 1.0 equiv) 2-phenyl-1-butanol **1b** (0.60 mL, 3.9 mmol, 1.0 equiv) and DMAP (27 mg, 0.22 mmol, 5 mol %) in DCM (22 mL) to give the crude product as a colourless oil. Purification by column chromatography on silica gel using hexane/ethyl acetate (95:5) as eluent gave pure ester **2e** (0.428 g, 50%) as a colourless oil. IR (neat): $\bar{\nu}$ = 2969 (C—H), 1732 (C=O), 1190, 1153 (C—O), 699 (C—H Ar) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 [t, *J* = 7.4 Hz, 3H, CH$_2$CH_3), 1.06 [d, *J* = 7.0 Hz, 3H, CH(CH_3)$_2$], 1.09 [d, *J* = 7.0 Hz, 3H, CH(CH_3)$_2$], 1.52–1.71 [m, 2H, CH_2CH$_3$], 2.47 [sept, *J* = 7.0, 1H, *C*H(CH$_3$)$_2$], 2.75–2.92 [sym m, 1H, *C*HCH$_2$O], 4.21 [d, *J* = 7.0 Hz, 2H, C(1)H_2], 7.00–7.48 [m, 5H, Ar-*H*] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.8 [*C*(4)H$_3$], 18.9 [CH(*C*H$_3$)$_2$], 25.3 [*C*(3)H$_2$], 34.0 [*C*H(CH$_3$)$_2$], 46.8 [*C*(2)H], 68.0 [*C*(1)H$_2$], 126.6, 128.0, 128.4 [3 × Aromatic *C*H], 141.9 [4° Aromatic *C*], 177.1 [*C*=O] ppm. HRMS (ES+) calcd for [$C_{14}H_{21}O_2$]$^+$: 221.1542; found: 221.1537. HPLC: Chiralcel OJH, 2:98 (2-propanol/hexane), 1 ml/min.

RT = 6.1 min, 8.3 min. This compound is novel and has been fully characterised.

4.9. 3-Methyl-2-phenylbutyl isobutyrate 2f

Prepared following the procedure for **2b** using anhydrous pyridine (0.31 mL, 0.304 g, 3.8 mmol, 1.5 equiv), isobutyryl chloride **3d** (0.27 mL, 2.6 mmol, 1.0 equiv), 3-methyl-2-phenyl-1-butanol **1c** (0.413 g, 2.5 mmol, 1.0 equiv) and DMAP (16 mg, 0.13 mmol, 5 mol %) in DCM (10 mL) to give the crude product as a colourless oil. Purification by column chromatography on silica gel using hexane/ethyl acetate (95:5) as eluent gave pure ester **2f** (0.212 g, 35%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 [d, J = 6.7 Hz, 3H, C(4)H_3], 0.89–1.10 [m, 9H, C(4)H_3 and CH(CH_3)$_2$], 1.88–2.10 [m, 1H, $CH_2CH(CH_3)_2$], 2.41 [sept, J = 7.0 Hz, 1H, COCH(CH_3)$_2$], 2.57–2.79 [sym m, CHCH_2O], 1H, 4.35 [d, J = 6.8 Hz, 2H, C(1)H_2], 7.00–7.48 [m, 5H, Ar-H] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.8, 20.7, 20.9 [3× CH_3 signals for 4× CH_3], 30.4 [C(3)H], 34.0 [COCH], 51.8 [C(2)H], 66.2 [C(1)H_2], 126.4, 128.1, 128.5 [3 × Aromatic CH], 141.6 [4 °Aromatic C], 177.1 [C=O] ppm. IR (neat): 2969 (C—H), 1732 (C=O), 1190, 1154 (C—O), 700 (C—H Ar) cm^{-1}. HRMS (ES+) calcd for $[C_{15}H_{23}O_2]^+$: 235.1698; found: 235.1687. HPLC: Chiralcel OJH, 1:99 (2-propanol/hexane), 1 ml/min. RT = 6.0 min, 8.4 min. This compound is novel and has been fully characterised.

4.10. Preparative scale lipase mediated hydrolysis of 2-phenylpropyl isobutyrate 2d

Candida antarctica Lipase B (immobilised) (52 mg, 25% w/w) was added to a solution of 2-phenylpropyl isobutyrate **2d** (200 mg, 1 mmol) in phosphate buffer (0.1 M, pH 7, 10 mL) and *tert*-butanol (1.7 mL, 17% v/v). The solution was sealed in a conical flask and shaken at 750 rpm for 72 h. The reaction mixture was filtered through Celite® to remove the lipase, and washed with diethyl ether (5 × 10 mL). The resulting solution was separated and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The organic layers were combined and washed with brine (50 mL) and concentrated to give a crude mixture of alcohol (*S*)-**1** and ester (*R*)-**2d** (43% conversion, ee_s = 65%, ee_p = 86%). The mixture was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent (95:5) to give the pure ester (*R*)-**2d** (106 mg, 0.54 mmol, 53%) as a colourless oil $[\alpha]_D^{20} = -24.2$ (*c* 0.72, methanol), 70% *ee* and the pure alcohol (*S*)-**1a** (45 mg, 0.33 mmol, 34%) as a colourless oil $[\alpha]_D^{20} = -119.5$ (*c* 0.2, methanol), 90% *ee*. ^{1}H NMR data for the enantioenriched (*R*)-**2d** were identical to that of the racemic sample previously described. Data for (*S*)-**1a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 [d, J = 7.1 Hz, 3H, CH(CH_3)$_2$], 1.73 [broad s, 1H, OH], 2.75–3.05 [sym m, 1H, CH(CH$_3$)], 3.65 [d, J = 7.1 Hz, 2H, CH_2OH], 7.10–7.43 [m, 5H, Ar-H] ppm.

4.11. Methyl 3-methyl-2-phenylbutanoate 5[51]

A sample of potassium *tert*-butoxide (8.705 g, 77.7 mmol) was suspended in dry DMF (100 mL) at 0 °C under a nitrogen atmosphere and methyl phenylacetate **4** (9.4 mL, 10 g, 66.6 mmol) was added at once, followed by isopropyl bromide (6.30 mL, 8.25 g, 67.1 mmol) after 2 min. The ice bath was removed and the reaction allowed to warm to room temperature (ca. 20 °C) and stirring was continued for 1 h. The reaction was quenched with water (50 mL) and DCM (40 mL), and stirred overnight. The solution was extracted with DCM (2 × 40 mL). The organic layer was washed with satd aq NH_4Cl solution (40 mL) and water (40 mL), dried, filtered and concentrated to give crude **5** as a pale yellow oil. Purification by column chromatography on silica gel using hexane/diethyl ether (90:10) as eluent gave pure ester **5** (8.358 g, 68%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 [d, J = 6.6 Hz, 3H, C(4)H_3], 1.03 [d, J = 6.6 Hz, 3H, C(4)H_3], 2.25–2.45 [m, 1H, C(3)H], 3.15 [d, J = 10.5 Hz, 1H, C(2)H], 3.65 [s, 3H, OCH_3], 7.18–7.41 [m, 5H, Ar-H] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.2 [C(4)H$_3$], 21.5 [C(4)H$_3$], 28.0 [C(2)H], 51.7 [OCH$_3$], 60.0 [C(1)], 127.2, 128.4, 128.5, [3 × Aromatic CH], 138.4, [4° Aromatic C], 174.4 [C=O] ppm. All data is in agreement with previously reported data.

4.12. 3-Methyl-2-phenylbutan-1-ol 1c[51]

Methyl 3-methyl-2-phenylbutanoate **5** (8.0 g, 41.6 mmol) in diethyl ether (40 mL) was added slowly to a stirring suspension of $LiAlH_4$ (3.30 g, 87.0 mmol) in diethyl ether (80 mL). The reaction was monitored by TLC and after complete consumption of the ester (6 h), the reaction was quenched with ethyl acetate (40 mL). The solution was stirred, water (40 mL) was added and the volatiles removed. The layers were separated and the aqueous layer was extracted with DCM (3× 100 mL). The combined organic layers were washed with brine (100 mL), dried, filtered and concentrated to give the crude alcohol **1c** (6.83 g, 100%) as a colourless oil. The product was used without purification. IR (neat): 3368 (OH), 2957 (C—H), 1494, 1453, 1366, 1056, 1031, 699 (C—H) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74 [d, J = 6.9 Hz, 3H, C(4)H_3], 0.99 [d, J = 6.9 Hz, 3H, C(4)H_3], 1.82–2.03 [m, 1H, C(3)H], 2.51 [td, J = 8.7 Hz, 5.0 Hz, 1H, C(2)H_2], 3.72–4.02 [m, 2H, C(1)H_2], 7.16–7.37 [m, 5H, Ar-H] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.0 [2× CH_3], 30.1 [C(3)H], 55.8 [C(2)H], 65.2 [C(1)H_2], 126.7, 128.5, 128.7 [3× Aromatic CH], 141.7 [4° Aromatic C] ppm. HPLC: Chiralcel OJH, 1:99 (2-propanol/hexane), 1 ml/min. RT = 21.9 min, 28.2 min. All data is in agreement with previously reported data.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.08.002.

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