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Catalysis

Enantioselective Enzymatic Synthesis of (*R*)-Phenyl Alkyl Esters and Their Analogue Amides using Fatty Acids as Green Acyl Donors.

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An efficient enantioselective synthesis of a set of (*R*)-phenylalkylesters and their analogues amides *via* enzymatic acylation of 1-phenylethanol (*rac*-**1**) and 1-phenylethanamine (*rac*-**2**) using carboxylic acids with different chain-lengths as green acyl donor is reported. Three lipases are used: *Candida antarctica* B immobilized on acrylic resin (*CAL-B*) and two free lipases: *Pseudomonas cepacia* (*PCL*) and *Candida rugosa* (*CRL*). The *CAL-B* shows an excellent selectivity during the acylation of *rac*-**1** without restriction due to the acyl carbon chain-length, the (*R*)- esters (**1 a**–**1 f**) were obtained enantiopures (ee up to 99 %). For the first time, the *PCL* catalyzed *O*-acylation allows smoothly to (*R*)-(**1 d**–**1 f**) with high selectivity (E⋙200) is described. The conversions increase with the length of the carbon-chain of the acyl donor (28.7 % ≤ C ≤ 40 %). The *CRL* shows less selective and provided the (*R*) (**1 b**–**1 e**) with 77 % ≤ ee_p ≤ 86.4 %. Due to its high thermostability, the *CAL-B* is used for the *N*-acylation of *rac*-**2** and provides access to enantioenriched (*R*)-fatty amides (**2 d**–**2 f**) (60.7 % ≤ ee_p ≤ 74.4 %) and the remained (*S*)-2 with ee_s > 91 %.

Introduction

Nowadays, biocatalysis is considering as the most attractive, clean and sustainable route to reach enantioenriched building blocks in numerous industries and exhibit significant biological activities, such as: the production of active pharmaceutical ingredients (APIs), cosmetics and flavour, agricultural and valuable fine chemicals.[1] Lipases (triacylglycerol acyl hydrolases, EC.3.1.1.3) are the most exploited enzymes for their easy use, mild conditions, recyclability, and biodegradability, without the use of cofactors, excellent stability in organic solvents and for their remarkable *chemo*-, *regio*- and *enantio*-selectivity. For all these advantages, technical and environmental, those robust biotools are effective to access enantiomerically pure compounds, mainly by kinetic resolution of racemates.[2] Enantioenriched molecules bearing hydroxyl- or amine functionalities on the α-stereogenic carbon are present in many pharmacologically active compounds.[3] The (*R*)-α-phenylethanol is used as chiral building block and synthetic intermediate in the fine-chemical and pharmaceutical industries. Their derivatives esters produced by microbial or enzymatic methods are labeled as natural in accordance with the United States and European Legislations, thereby satisfying the consumer trend towards natural products in various industries.[4] The enantiopure substituted α-methylbenzylamine are also important molecular building blocks, used as, a raw material for the preparation of optically active drugs (Ketorolac, Rivastigmine, Rasagiline mesylate, Labetalol, the DMP 777 an inhibitor of leukocyte elastase, …etc).[5]

Lipase mediated *O*-acylation of secondary alcohols and *N*-acylation of primary amine *via* kinetic resolution in organic medium consists the target way to obtain them and their derivatives esters and amides under optically active form.[6] Despite the higher nucleophilicity of primary amines compared to alcohols, the enzymatic resolution of secondary alcohols still the most studied compared to the amines one.[7]

In this context, versatile biocatalytic processes have explored, to reach several enantiopure secondary alcohols and their acetate derivatives by enzymatic kinetic acylation and deacylation.[8] Previously, we have described that the lipases efficiency was multifactorial and several parameters interact simultaneously, nature and the amount of lipase,[9] nature of solvent,[10] introduction of additives[11] and especially the nature of the acetylating agent[12] controlling both reactivity and selectivity. In order to circumvent of the reversibility issue of the enzymatic kinetic resolution reactions, the choice of the acyl donor still decisive. Whereas, for the *N*-acylation: fatty esters, *o*-methoxyesters or dialkylcarbonates are usually em-

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ployed as acyl donors, for the *O*-acylation, enol esters and anhydrides are scarcely used.[13]

The use of carboxylic acids as acylating agents in biotransformation is a powerful tool that opens new opportunities towards green process.[13a] Carboxylic acids are more benign and environmentally friendly than other common acyl donors; they open up novel opportunities towards green chemistry provided that an efficient water removal protocol is applied. The use of them as acylating agents in enzymatic reactions is still limited despite their advantages on the greenness process scale, mainly: free-waste biotransformation (the one waste is water), recyclable and biodegradable catalyst. Furthermore, they are natural substrates for lipases; they are inexpensive and available.[14] Fatty carboxylic acids are used to increase the lipophilic character of some pharmaceuticals, such as: phenol derivatives,[15] flavonoids,[16] aminoalcohols.[17]

The use of fatty carboxylic acids for the enantioselective *O*-acylation and *N*-acylation still modestly reported, and the most commonly used lipase is the immobilized *Candida Antarctica lipase* (*CAL-B*).[18] In this context, a kinetic study of the *O*-acylation and *N*-acylation of monofuctional 2-butanol and sec-butylamine using myristic acid catalyzed by *CAL-B* has been reported with low selectivity factor.[19]

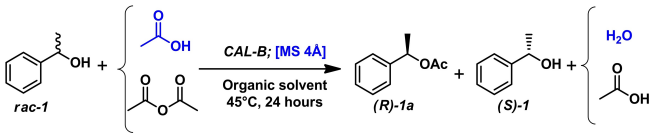
In the present paper, we describe the use of several alkyl carboxylic acids species, especially fatty acids to achieving a facile and clean preparation of enantiopures esters and amides. Impact of these green acyl donors on the stability, reactivity and the selectivity of three lipases during the acylation of *rac*-1-phenylethanamine and the *rac*-1-phenylethanol is studied. The used lipases are: the *candida antarctica* lipase fraction B immobilized on acrylic resin (*CAL-B*) and two free lipases: the *pseudomonas cepacia lipase* (*PCL*) and the *candida rugosa lipase* (*CRL*).

At the best of our knowledge, the enzymatic kinetic resolution of 1-phenylethanol using non activated fatty carboxylic acids by means of the free lipases *PCL* and *CRL* are not described yet, only their immobilized forms are used for the esterification of glycerols.[20] At the best of our knowledge, with the exception using decanoic acid in enzymatic kinetic resolution of 1-phenylethanol[21] and in ionic liquid for the 1-phenylethan-amine,[22] and that under *vacuum*, this approach has been little described.[23] Furthermore, if the chain-length of substrate and its effect on the selectivity of various lipases has been studied, it is especially the effect of alcohol chain-length on enzymatic esterification is the most studied.[7a]

Results and Discussion

Firstly, the feasibility of the direct acylation of 1-phenylethanol with acetic acid as acyl donor, in the presence of the *CAL-B* was checked. Experiments were performed in several organic media to examine the impact of acetic acid and verify its influence as by-product using the anhydride of acid as acyl donors (Scheme 1).

The acylation of 1-phenylethanol (*rac*-**1**) using acetic acid was selected as reaction model to control the efficiency of the *CAL-B* in several organic solvents with different logP values



Scheme 1. Lipase catalyzed *O*-acylation of 1-phenylethanol: *Solvent strategy.*

(Solvent's polarity or hydrophobicity logP: the partition coefficient of the employed solvent between water and octanol in a two-phase system). It is well known that for biotechnological purpose, the use of organic solvent poor in water enhanced lipase thermostability, thermodynamic equilibrium shifted towards ester synthesis. For that, hydrophobic solvents are selected, and the molecular sieves 4 Å, is used as water-controlling environment.[14b] For better comprehension of the impact of this acylating agent, a comparison was done using their corresponding acetic anhydride.

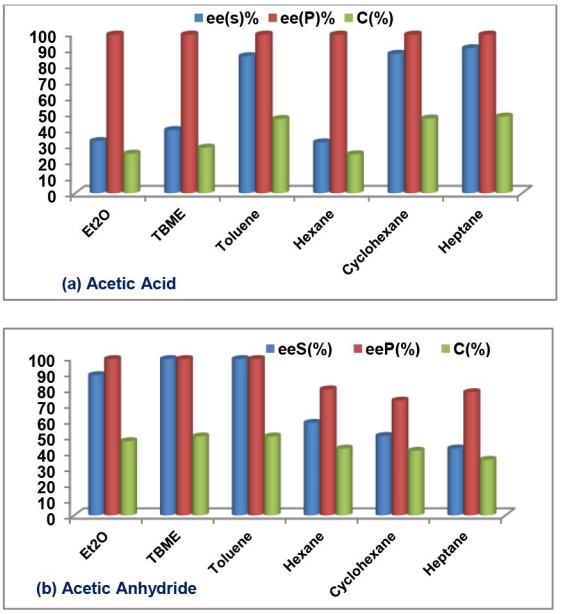
All the experiments were carried out on equimolecular mixture of *rac*-**1** and acyl donor, diluted in 5 mL of organic solvent, in the presence of 40 mg of *CAL-B*. The used solvents are: Diethylether (Et_2O) (logP = 0.85), *t*-butylmethylether (TBME) (0.35), Toluene (2.52), Cyclohexane (3.2), Hexane (3.9) and Heptane (4). The reactions were stirred at 45 °C for 24 hours.

For the experiments with acetic acid 60 mg of molecular sieves 4 Å are added. The evolution of the reactions was monitored by TLC. The reactions mixtures were filtered then evaporated in *vaccum*. The conversions (C) and the enantiomeric excesses of furnished acetates (*R*)-***1a*** (ee_p) and the remained alcohols (*S*)-***1*** (ee_s) were quantified by chiral GC analysis of samples of 50 µL of the reactions mixtures. The obtained results were summarized in Figure 1.

The impact of the hydrophobicity of the employed organic solvent was significantly observed on the reaction rates and on the enantioselectivity depending to the used acyl donor.

Using acetic acid as acyl donor, a high selectivity ($E \gg 200$) in favour of the (*R*)-enantiomer was recorded in all organic solvents used (Figure 1). The use of less hydrophobic solvents doesn't affect the *CAL-B* enantioslectivity. The highest conversions were recorded in solvents with $logP > 2.5$ and the best conversion ($C = 47.8\%$) was achieved in heptane ($logP = 4$) within 24 hours. Very close conversions were reached in toluene and cyclohexane but after 48 hours.

When acetic anhydride was used, the solvent hydrophobicity intervenes differently on both reactivity and selectivity of the *CAL-B*. High conversions and selectivities were recorded in less hydrophobic solvents ($logP < 2$). Ideal enzymatic kinetic resolutions were obtained in toluene and TBME ($E \ggg 200$, $C = 50\%$). Whereas, in more hydrophobic solvents (Hexane, cyclohexane and heptane) a significant decrease in conversion rates ($35\% \leq C \leq 42\%$) with drastic chute of the selectivity factor ($10 \leq E \leq 16$) were observed. The results obtained revealed a significant impact of the nature of the acyl donors on the selectivity of the acylation catalyzed by *CAL-B* which strongly depends on the hydrophobicity of the organic medium.



[a]1mmole of *rac*-1, 1mmole of acetic acid, 40 mg of *CAL-B* and 60 mg of molecular sieves 4Å diluted in 5mL of organic solvent and stirred at 45°C for 24 hours. [b] 1mmole of *rac*-1, 1mmole of acetic anhydride, 40 mg of *CAL-B* diluted in 5mL of organic solvent and stirred at 45 °C for 24 hours. [c] Enantiomeric excess are measured by chiral GC ee=|R-S|/|R+S|. [d] Conversion : C = ee_S/ee_P+ee_s ; Selectivity: E = Ln [(1-C) (1-$ee_{(S)}$)]/ Ln [(1-C) (1+$ee_{(S)}$)].[24]

Figure 1. *CAL-B* catalyzed *O*-acylation of *rac*-1 using acetic acid and acetic anhydride.

On the other hand, the generation of acetic acid as byproduct when the acetic anhydride was used impacts the performance of *CAL-B*, and that, in more hydrophobic media such as hexane, cyclohexane and heptane. Thus, the use of acetic acid as an acyl donor has given the best results in all the organic solvents used. The study will continue under these conditions with heptane as organic solvent, and that for two raisons: the better dissociation of weak organic acids, and the removal of the micro-aqueous layer around the lipase, which in turn sustains essentially the structure and the catalytically active conformation of lipases.[25]

To evaluate another time the feasibility of this biotransformation, we have checking the shift of the reaction in the desired side, for that the kinetic profile of the direct esterification in heptane was established. The experiment conditions was undertaken using 6 mmoles of *rac*-**1** and the outcome of the esterification was monitored by GC analysis of aliquots of 50 µL of the reaction mixture, beforehand, filtered on silica gel. Figure 2 illustrates that the enantiomeric excesses of the residual enantiomer (*S*)-**1** were enhanced proportionally with the conversion rate. The enantiomeric excess of the produced enantiomer (*R*)-**1a** still steady overcome the acyl-transfer reaction. Hence, we validate the efficiency of the above determined experimental conditions.

The optimal developed conditions were applied to the *O*-acylation of 1-phenylethanol and extended over several

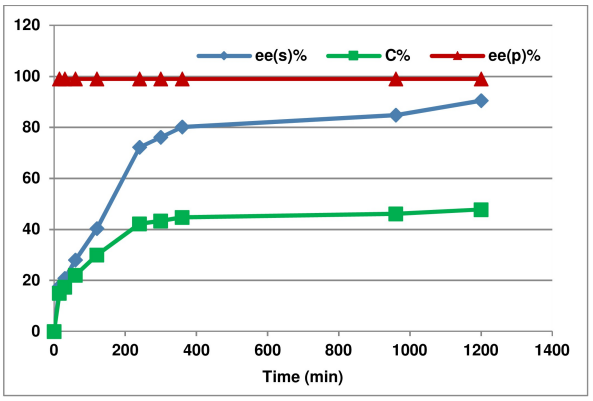
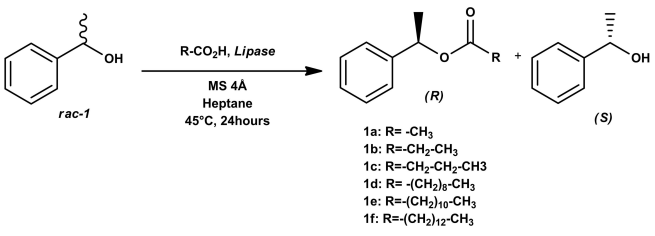


Figure 2. Kinetic profile of *CAL-B* catalyzed *O*-Acylation of *rac*-1 with acetic acid in heptanes.

aliphatic carboxylic acids of different chain length, and that, in the main aim to reach easily a set of natural enantiopures flavouring agents (**1a**–**1f**) under sustainable conditions. The behaviour's of three lipases are checked: the immobilized *CAL-B*, the free *PCL* and *CRL* in a hydrophobic medium. (Scheme 2)

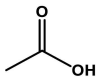
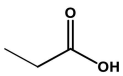
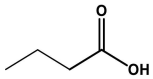
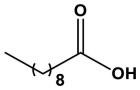
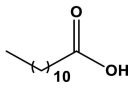
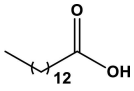
For thus, we have selected a series of fatty acids: propanoic acid, butyric acid, capric acid (decanoic), lauric acid (dodecanoic) and myristic acid (tetradecanoic). The reactions were carried out using equimolecular mixture of *rac*-**1** and the appropriate carboxylic acid (1mmole), in the presence of the appropriate amount of the indicated lipase. After 24 hours, the reactions mixtures were filtered then evaporated in *vacuum*. The enantiomeric excesses of produced esters (*R*)-(**1a**–**1f**) and remaining (*S*)-***1*** alcohols were quantified by chiral GC analysis. The yields were obtained after flash chromatography. The absolute configurations of all chiral compounds were determined by the comparison of the optical rotation measured with the literature data.

As shown on table 1, using the *CAL-B*, as biocatalyst, all the (*R*)-fatty esters were obtained enantiopures ($ee_p > 99\%$) and that, regardless to the carbon-chain length of the acyl donors ($E \gg 200$) and with good conversions ($45.5\% \leq C \leq 48.5\%$) (Entries 1, 4, 7, 10, 13 and 16). This lipase is known for its affinity toward longer chain fatty acids, in the present study, this preference has been confirmed, not only for the highest but also for the short chain lengths.



Scheme 2. Lipase catalyzed *O*-acylation of 1-phenylethanol with aliphatic carboxylic acids.

Table 1. Lipase catalyzed *O*-acylation of ***rac-1*** using carboxylic acids.

Entry	Carboxylic acid	Lipase	ee_P (%)[d]	Yield (%)[f]	ee_S(%)[d]	Yield (%)[f]	C (%)[e]	E[e]
1		*CAL-B*[a]	>99	44	90	44	48	≫200
2		*PCL*[b]	–	–	–	–	NR	–
3		*CRL*[c]	–	–	–	–	NR	–
4		*CAL-B*[a]	>99	44	88	43	47	≫200
5		*PCL*[b]	–	–	–	–	NR	–
6		*CRL*[c]	–	–	–	–	NR	–
7		*CAL-B*[a]	>99	43	87	46	46.8	≫200
8		*PCL*[b]	–	–	–	–	NR	–
9		*CRL*[c]	86.4	30	56.4	60	39.5	24
10		*CAL-B*[a]	>99	40	82.8	50	45.5	≫200
11		*PCL*[b]	>99	25	39.8	50	28.7	≫200
12		*CRL*[c]	83	35	75	38	47.5	24
13		*CAL-B*[a]	>99	40	82.8	50	45.5	≫200
14		*PCL*[b]	>99	25	45.8	55	31.6	≫200
15		*CRL*[c]	84.6	32	56.8	50	40.2	21
16		*CAL-B*[a]	>99	45	93.3	40	48.5	≫200
17		*PCL*[b]	>99	37	65.8	38	40	≫200
18		*CRL*[c]	–	–	–	–	NR	–

[a] 1mmole of *rac*-1, 1mmole of carboxylic acid, 40 mg of *CAL-B* and 60 mg of molecular sieves 4 Å diluted in 5 mL of organic solvent and stirred at 45 °C. [b]1mmole of *rac*-1, 1mmole of carboxylic acid, 100 mg of *PCL* and 60 mg of molecular sieves 4 Å diluted in 5 mL of organic solvent and stirred at 45 °C. [c] 1mmole of *rac*-1, 1mmole of carboxylic acid, 100 mg of *CRL* and 60 mg of molecular sieves 4 Å diluted in 5 mL of organic solvent and stirred at 45 °C. [d] Enantiomeric excess are measured by chiral GC: ee = |R–S|/|R+S|. [e] Conversion: $C = ee_S/ee_P + ee_S$; Selectivity: $E = Ln[(1-C)(1-ee_{(S)})]/Ln[(1-C)(1+ee_{(S)})]$.[24] [f] Isolated yield after separation on flash chromatography. **NR**: No reaction.

Whereas, no reactivity was shown using the *PCL* as biocatalyst with acids having short chain lengths: acetic, propionic and butyric acids (entries 2, 5 and 8). The corresponding fatty esters of capric (**6 d**), lauric (**6 e**) and myristic acids (**6 f**) were obtained enantiopures with high selectivity ($ee_p > 99\%$, $E \gg 200$) (Table 1, entries 11, 14 and 17) and conversions increase with the length of the carbon-chain of the acyl donor; from C:10 to C:14, the conversion rate jump from 28.7% to 40% (Table 1, entries: 11, 14 and 17). At the best of our knowledge, the obtained results with this lipase, using fatty acids as acyl donors are reported for the first time.

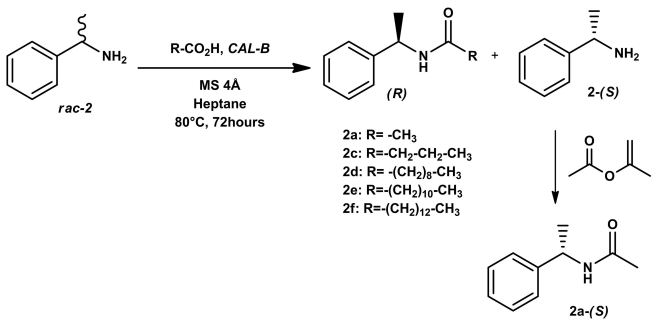
On the other hand, the recorded results with the *CRL* are in perfect accordance with the literature towards longer-chain fatty acids.[26] In the present work, additionally to myristic acid, we have proved that this lipase is not reactive using acetic or propionic acids as acyl donors (entry 18 *versus* 3 and 6). The enantioenriched (*R*)-fatty esters (**1 c**–**1 e**) were obtained with very moderate selectivity ($21 \leq E \leq 24$) at average conversion ($C > 39\%$) (entries 9, 12 and 15). Similar observations were noted in previous study, using vinyl acetates as acyl donors.[26]

The obtained results depend on the shape of the active sites of the three used lipases. It is established that the acyl binding site and the form of the lipases may be enough to accommodate a defined length of the acyl group. The active site of the *CAL-B* and the *PCL* has a funnel-shaped, that of the last one is the wider one, whilst, for the *CRL* it has tunnel shaped.[27]

Finally, it can be said that we are able to get a set of enantiopures floral esters using labelled natural process using biocatalytic reaction and green natural acyl donors. At the best of our knowledge the (*R*)-**1 f** derivative was obtained enantiopure for the first time under the described conditions. From the three exploited lipases, the *CAL-B* was the most suitable biocatalyst for this biotransformation and the *PCL* was a more active lipase for the longer-chain fatty acids.

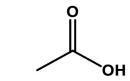
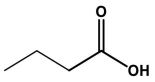
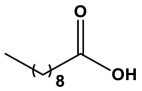
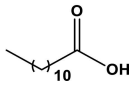
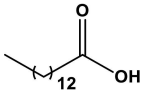
The obtained results in *O*-acylation with fatty acids as an acyl donor were then exploited to study the *N*-acylation of 1-phenylethanamine *rac-**2*** and access a variety of valuable enantioenriched fatty amides.

We have chosen *CAL-B* which is the most efficient lipase and thermostable, properties necessary for the feasibility of the reaction. All experiments were performed on an equimolecular mixture of *rac-**2*** and appropriate carboxylic acid in the presence of 50 mg of *CAL-B* with 50 mg of molecular sieves diluted in 2 mL of heptane. After 72 hours of stirring at 80 °C, the mixture is diluted in ethyl acetate and filtered (Scheme 3). The formed amides and the residual amines were separated by



Scheme 3. *CAL-B* catalyzed *N*-Acylation of 1-phenylethan-amine using fatty acids.

Table 2. *CAL-B* catalyzed *N*-Acylation of 1-phenylethanamine with aliphatic carboxylic acids.

Entry [a]	Carboxylic acid	ee_P(%) [b]	Yield% [d]	ee_s(%)[b]	Yield% [d]	C (%) [c]	E [c]
1		5.8	36	7	30	55	1
2		52.5	40	56.4	28	51.8	5
3		70.6	42	> 99	25	58.4	29
4		74.4	35	91	30	45	49
5		60.7	46	> 99	20	60.7	22.5

[a] 1mmole of *rac*-2, 1mmole of carboxylic acid, 50 mg of *CAL-B* and 50 mg of molecular sieves 4 Å diluted in 2 mL of heptane and stirred at 80 °C for 72 hours. [b] Enantiomeric excess are measured by chiral HPLC $ee = |R–S|/|R+S|$. [c] Conversion: $C = ee_S/ee_P + ee_s$; Selectivity: $E = Ln[(1-C)(1-ee_{(S)})]/Ln[(1-C)(1+ee_{(S)})]$.[24] [d] Isolated yield after separation by liq-liq extraction.

acido-basic liquid-liquid extraction. The remained amines (*S*)-**2** were subjected to a derivatization to acetamide form (*S*)-**2a** using enol esters under free-solvent conditions. The conversions and the enantiomeric excesses of the (*S*)-**2a** and the furnished (*R*)-(**2a**–**2f**) were determined by chiral HPLC. All the obtained results are summarized in Table 2.

The *CAL-B* catalyzed *N*-acylation of *rac*-**2** using carboxylic acids is rather less enantioselective compared to *O*-acylation. The selectivity factor varied from E = 1 with acetic acid to E = 49 with the lauric acid (Table 2, entry 1 *versus* 5). The best result is obtained with lauric acid with a selectivity E = 49 and a conversion C = 45 % (Table 2, entry 4). No significant influence was observed on the lipase *CAL-B* reactivity but the length of the carbon chain strongly impacts the selectivity of CAL–B lipase (Table 2, entries 1, 2 *versus* 3, 4, 5)

The (*R*)-fatty amides (**2d**–**2f**) were obtained with enantiomeric excesses values of $60.7\% \leq ee_p \leq 74.4\%$ and the remained (*S*)-**2** with enantiomeric excesses values of $91\% \leq ee_s \leq 99\%$ (Table 2, entries 3–5).

At the best of our knowledge, using fatty acids as acyl donors are reported for the first time for the enzymatic kinetic resolution (EKR) of 1-phenylethanamine under the described conditions, and it is to be underlined that *N*-((*S*)-1-phenylethyl)dodecanamide (**2f**) was known for their use for the treatment and prevention of bacterial damages and diseases.[28]

Conclusion

Carboxylic acids with various carbon-chain lengths were effectively used as green acyl donor with lipases in *O*-acylation of *rac*-phenylethanol **1** and *N*-acylation of *rac*-phenylethanamine **2**, and that to reach enantiopure fatty esters and their analogues amides of high added values. Three lipases were examined: the immobilized *CAL-B*, the *PCL* and the *CRL*. Only the first one was effective for both acyl transfer reactions. With lipase *CAL-B*, the *O*-acylation of *rac*-**1** allows to reach all the (*R*)-phenyl alkyl esters (**1a**–**1f**) enantiopures ($ee_p > 99\%$) and that, regardless to the carbon-chain length of carboxylic acid with excellent selectivity ($E \gg 200$) at high conversions. On the other hand, the lipase *PCL* show a high affinity only toward fatty esters (**1d**–**1f**), the best results was obtained using myristic acid as acyl donor (C = 40 %, $E \gg 200$). The obtained results using free *PCL* are reported for the first time. For the *N*-acylation, only the (*R*)-fatty amides (**2d**–**2f**) were obtained with acceptable enantiomeric excesses ($60.7\% \leq ee_p \leq 74.4\%$).

The generation of water as the only byproduct makes the use of carboxylic acids an ideal acylating agent for environmentally and a financially options for the industry. We were able to obtain a set of enantiopure form of floral esters using labelled natural process by means of biocatalytic reaction and green natural acyl donors. In short, our method is simple, green and highly enantioselective.

Supporting Information Summary

Supporting information file includes the general experimental procedure, compound characterization data and the ^1H and ^{13}C spectra of all compounds. The optical rotations of all esters and amides measurement, the chiral GC conditions of all compounds and their chromatograms are also given in this section.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Acylation · Fatty acids · Sustainable biocatalysis · *CAL-B* · *PCL* · *CRL*

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