Graphical Abstract.

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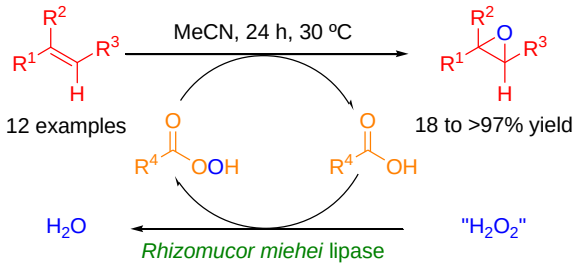

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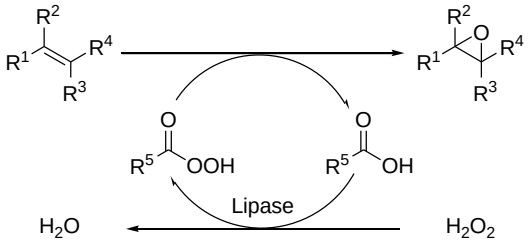
ABSTRACT

A chemoenzymatic and selective method for the epoxidation of a series of cyclic and lineal alkenes is described. Epoxides have been obtained in moderate to excellent conversions under mild reaction conditions through a two-step sequence, carried out in *one-pot*. This chemoenzymatic approach is based on a *Rhizomucor miehei* lipase-catalyzed perhydrolysis reaction to form the corresponding peracid, and subsequent epoxidation of the corresponding alkenes. Reaction parameters with influence in the biotransformation have been optimized specially focusing in the efficient enzymatic peracid formation by means of the correct choice of solvent, oxidant and peracid precursor. This chemoenzymatic approach has been efficiently applied for the first time, in the regioselective chemical oxidation of (*S*)-carvone and limonene, both showing an opposite behavior for the oxidation of the internal and external C-C double bond, respectively.

1. Introduction

Epoxides represent an important class of oxygenated heterocycles with multiple applications in the fine chemical industry for the production of adhesives, coating, paints and polymers. Additionally, they are considered as versatile synthetic intermediates towards alcohols, alkenes, diols and other families of interesting organic compounds. Traditionally epoxides have been smoothly prepared through heterogeneous or homogeneous catalytic alkene epoxidation, using metal catalysts, organic peroxides or peracids for non enzymatic transformations,[1] while monooxygenases or chlorperoxidases have been employed in biotransformations. Remarkably, the asymmetric version has received great attention in the last decades for the production of the desired epoxides generally with excellent yields and enantiomeric excess.[2]

One of the most common strategies for the synthesis of epoxides is based on *in situ* peracid formation (perhydrolysis), which can be achieved by reaction of a carboxylic acid or ester with hydrogen peroxide or their derivatives as oxidants. From an environmental point of view, hydrogen peroxide is a preferred oxidant since the transformation gives only water as by-product. In this context, the enzymatic-catalyzed epoxidation of alkenes has been successfully achieved using hydrolases such as perhydrolases, lipases, esterases and acyl transferases.[3] For this type of transformation, also called Prileshajev epoxidation, lipases are usually the biocatalyst of choice, especially since Bjorkling and co-workers described their applicability for the first time in 1990 (Scheme 1).[4] This is a very practical reaction as combines in *one-pot*, the oxidation of the carboxylic acid or ester to the peracid, which is the responsible for the chemical oxidation of the alkene. In this manner, peracid storage and transportation is not required, providing a safe strategy for the development of different oxidative transformations,[5] such as consecutive epoxidation and esterification reactions,[6] Baeyer Villiger oxidation of cyclic ketones[7] or lignocelluloses delignification.[8] Interestingly, some recent studies of this biocatalytic promiscuity behavior display by hydrolases[9] have concluded that the oxidation step is strictly a chemical step that occurs without the action of the enzyme, and for that reason non stereoselectivity is achieved.[3c] In fact, moderate to good stereoselectivities have been obtained when using chiral oxygen transferring agents.[10]



Scheme 1. Epoxidation of alkenes through lipase-catalyzed perhydrolysis of carboxylic acids.

The lipase-catalyzed approach can be considered as an indirect epoxidation reaction of alkenes, although some authors have demonstrated the potential of *Candida antractica* lipase type B (CAL-B) mutants for catalyzing the direct epoxidation of α,β-unsaturated aldehydes with hydrogen peroxide.[11] CAL-B[12]

and *Pseudomonas cepacia* lipase (PSL)[13] are probably the most versatile lipases for alkene epoxidation using a variety of peracid precursors. However little attention has been made to other hydrolases.[4,14] *Rhizomucor miehei* lipase (RML) is a commercially available enzyme in both soluble and immobilized form, which has shown excellent activities in a series of synthetic applications such as aminolysis, esterification or transesterification,[15] however its application in perhydrolysis reactions for the later formation of alkenes remains in a premature stage as negligible[4,14] or moderate[16] conversions were found by different authors, probably because of the inactivation of the enzyme at high hydrogen peroxide concentrations.

Herein, we wish to report the application of RML in the synthesis of a broad panel of epoxides, dealing with the optimization of several parameters with influence in the enzyme reactivity. Thus, the production of twelve epoxides in good overall yields through a two-step and *one-pot* process will be discussed, two of them in a selective fashion were the oxidation of the internal or external carbon-carbon double bond was achieved.

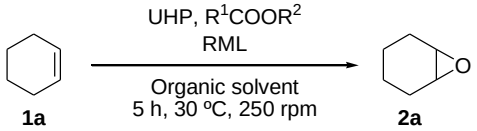
2. Results and discussion

The initial objective was to find the optimal conditions for the peracid formation. Cyclohexene (**1a**) was considered as a model substrate. because of its commercial availability and easiness in the monitoring of its epoxidation reaction by gas chromatography (GC). Different oxidants were used to carry out the oxidation reaction towards the formation of cyclohexene oxide (**2a**). Initially 4 equivalents of a 30% hydrogen peroxide aqueous solution were used in the presence of decanoic acid with a water: dichloromethane mixture (1:1.2 v/v) as solvent. Unfortunately deactivation of RML was rapidly observed, yielding **2a** in only 4% conversion after 24 h at 30 ºC. This result is far to be synthetically applicable in comparison with the complete conversion achieved with CAL-B as catalyst. The use of dimethyl carbonate[12c] as peracid precursor also led to negligible conversions. Then, hydrogen peroxide-urea complex (UHP) was used for the safe release of hydrogen peroxide into the medium, and a first screening was conducted trying to avoid the presence of great amounts of H_2O_2 that clearly deactivate RML (Table 1).

First, ethyl acetate was used as both solvent and carboxylic acid derivative to form the peracid, however only 5% conversion was achieved after a short time span of 5 h (entry 1). Then, different solvents were used in combination with decanoic acid and UHP, while tetrahydrofuran led to a very low conversion (entry 2), both 2-methyltetrahydrofuran and *tert*-butymethyl ether led to 16% (entries 3 and 4), the highest conversion being achieved with acetonitrile (entry 5). It must be mentioned that the reaction in the absence of enzyme led to negligible conversions in all cases.

The nature of carboxylic acid was then studied, finding that short-chain carboxylic acids (i.e. acetic acid or butyric acid, entries 6 and 7) did not serve as good intermediates for the peracid formation. The best result was found for lauric acid (31% conversion), containing two carbon atoms more than decanoic acid (entries 5 and 8), while a decrease in the conversion was found using a bigger one such as stearic acid (entry 9). In addition, no conversion was found for those containing aromatic rests in their structure (entries 10 and 11).

Table 1. Epoxidation of cyclohexene (**1a,** 0.33 M) using RML, carboxylic acids or EtOAc (1.1 eq) and UHP (1.1 eq) in different organic solvents at 30 ºC and 250 rpm after 5 h.

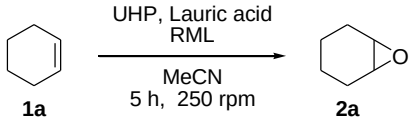


Entry	R^1COOR^2	Solvent	*c* (%)[a]
1	EtOAc	EtOAc	5
2	Decanoic acid	THF	4
3	Decanoic acid	2-Me-THF	16
4	Decanoic acid	TBME	16
5	Decanoic acid	MeCN	23
6	Acetic acid	MeCN	<3
7	Butanoic acid	MeCN	<3
8	Lauric acid	MeCN	31
9	Stearic acid	MeCN	20
10	Benzoic acid	MeCN	<3
11	Phenylacetic acid	MeCN	<3

[a] Conversion values determined by GC.

The effects of temperature and alkene concentration were later analyzed in depth trying to improve the conversion values reached with lauric acid for the epoxidation of cyclohexene. For that reason the best conditions previously found were used for the epoxidation of **1a**, which means 1.1 equivalents of lauric acid and UHP in acetonitrile (Table 2). The conversions found for the reactions at 37 ºC and 45 ºC were significantly lower in comparison with the transformation at 30 ºC (entries 1-3), fact probably related to the thermostability of RML. Remarkably, maintaining the temperature at 30 ºC but doubling the substrate concentration a 64% conversion into **2a** was reached after 5 h (entry 4), and 85% after 24 h (entries 5 and 6). However a decrease of reactivity was observed at higher concentrations (1 M of **1a**, entry 7).

Table 2. Epoxidation of cyclohexene (**1a**) using RML, lauric acid (1.1 eq) and UHP (1.1 eq) in MeCN at different concentrations and 250 rpm.



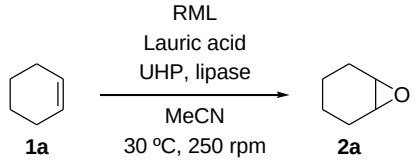
Entry	T (ºC)	[**1a**] (M)	t (h)	*c* (%)[a]
1	30	0.33	5	31
2	37	0.33	5	12
3	45	0.33	5	9
4	30	0.66	5	64
5	30	0.66	13	75
6	30	0.66	24	85
7	30	1	5	43

[a] Conversion values determined by GC.

Next, we decided to analyze the influence of both the UHP and lauric acid concentrations using different loadings of RML. The results have been summarized in Table 3. First, a clear

enzyme inhibition was observed at higher concentration of the oxidant UHP (entries 1 and 2), which is not surprising as that was previously observed when using the own hydrogen peroxide as oxidant. For that reason we decided to focus on different concentrations of lauric acid (0.2-1.1 eq.), observing that the reaction evolve efficiently towards the formation of the epoxide **2a** at higher concentrations of lauric acid (entries 3-8). In order, to reach better results the reaction was left for 24 h at both 1.1 and 2 equivalents of lauric acid, yielding 85 and 91% conversions, respectively (entries 9 and 10). However a 3-fold excess of lauric acid led to a poor solubility of the mixture in the reaction medium, leading to a significant lower conversion (68%, entry 11). Finally, it was demonstrated that the use of higher loadings of RML did not lead to an improvement in the conversion value after 24 h (entries 12 and 13).

Table 3. Epoxidation of cyclohexene (**1a**) using RML, lauric acid and UHP in MeCN at 30 ºC and 250 rpm.



1a **2a**

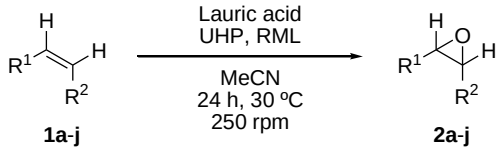
Entry	RML (mg)[a]	UHP (eq)	Lauric acid (eq)	[**1a**] (M)	*t* (h)	*c* (%)[b]
1	50	1.1	1.1	0.33	5	31
2	50	2	1.1	0.33	5	12
3	50	1.1	0.2	0.66	5	3
4	50	1.1	0.4	0.66	5	13
5	50	1.1	0.6	0.66	5	24
6	50	1.1	0.8	0.66	5	38
7	50	1.1	1.0	0.66	5	51
8	50	1.1	1.1	0.66	5	64
9	50	1.1	1.1	0.66	24	85
10	50	1.1	2	0.66	24	91
11	50	1.1	3	0.66	24	68
12	100	1.1	1.1	0.66	14	80
13	100	1.1	1.1	0.66	24	85

[a] Amount of RML in mgs for mmol of cyclohexene (**1a**).
[b] Conversion values determined by GC.

The oxidation of a range of epoxides is shown in Table 4, using the optimum conditions for the epoxidation of cyclohexene with RML, lauric acid and UHP. Gratifingly, the oxidation of cyclic substrates such as 2-methylcyclohexene (**1b**) and cyclohepetene (**1c**) occurred in quantitative yield after 24 h (entries 2 and 3), while dihydronaphtalene derivatives **2d**,**e** were obtained as major products with conversion up to 82% (entries 4 and 5), observing the formation of diol in 16% from **1e** by epoxidation and subsequent hydrolytic opening of the oxirane. A similar result was found for a linear alkene such as 4-octene (**1f**), obtaining the epoxide **2f** as major product in 80% (entry 6). Next, we decided to explore the potential of our oxidative system using styrene derivatives, observing a 54% conversion for the non substituted one (**1g**, entry 7), while a low reactivity was observed for styrenes **1h**-**j** bearing a bromo substituent in the aromatic ring. In these cases, the formation of epoxide was slighlty higher for the *para*-substituted (entries 8-10). Remarkably, similar results were achieved using magnetic stirring or orbital shaking in a 1 mmol scale. However, when the scale-up of the reaction was performed with 10 mmol of 1,4-dihydronaphtalene (**1d**), the reaction with magnetic stirring led to the same 82% conversion value, finding a slight decrease with orbital shaking conditions (62%).

One of the advantages when using immobilized enzymes, is the possibility to recover the enzyme at the end of the process for further applications. Enzyme recycling is a key issue in biotransformations especially for economic reasons. Unfortunately in the oxidation of 1,4-dihydronaphtalene (**1d**) the reuse of the RML led to a premature and dramatic decrease in activity. More than five-times lower activity was observed after two cycles and a complete loss of activity in the third one. These results suggest the denaturalization of the enzyme with a prolonged exposure to hydrogen peroxide.

Table 4. Epoxidation of alkenes **1a**-**j** (0.66 M) using RML (50 mg/mmol), lauric acid (2 eq) and UHP (1.1 eq) in MeCN at 30 ºC and 250 rpm after 24 h.



1a-j **2a-j**

Entry	Substrate	**2a-j** (%)[a]
1	Cyclohexene (**1a**)	91
2	2-Methyl-cyclohexene (**1b**)	>97
3	Cycloheptene (**1c**)	>97
4	1,4-Dihydronaphtalene (**1d**)	82
5	1,2-Dihydronaphtalene (**1e**)	83
6	4-Octene (**1f**)	80
7	Styrene (**1g**)	54
8	2-Bromo-Styrene (**1h**)	25
9	3-Bromo-Styrene (**1i**)	27
10	4-Bromo-Styrene (**1j**)	40

[a] Percentage of epoxide **2a**-j obtained from the corresponding alkene. Determined by GC.

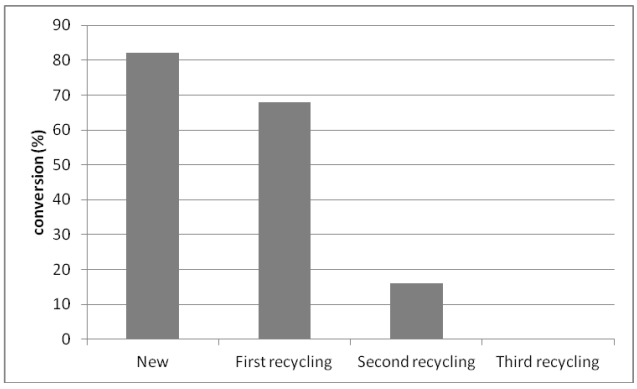
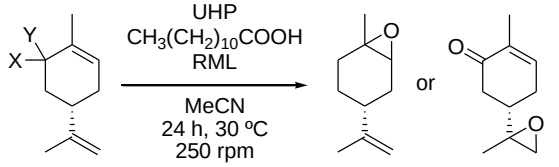


Figure 1. Study of the RML recycling using **1d**, lauric acid (2 eq) and UHP (1.1 eq) at 30 ºC during 24 h at 250 rpm.

Finally, we decided to explore the possibility to carry out regioselective oxidation processes, which can have potential applications in different areas such as the oxidation of terpenes. In fact, just a few examples have been published in this area related to the use of lipases for the indirect oxidation of C-C double bonds.[17] We selected compounds (*S*)-carvone and

limonene both having two C=C bonds in their structure, one inserted in a cyclic ring and other exocyclic (Table 5). Significantly limonene was oxidized using RML for the peracid formation, affording with 18% conversion the epoxide derived from the internal alkene bond oxidation as unique product (entry 1), while satisfyingly the oxidation of the exocyclic C=C bond of (*S*)-carvone was achieved with a more significant 78% conversion (entry 2). The epoxidation reactions of limonene and (*S*)-carvone using CAL-B were also run for comparison, finding similar results in terms of activity (entries 3 and 4)

Table 5. Epoxidation of limonene and (*S*)-carvone (0.66 M) using RML (50 mg/mmol), lauric acid (2 eq) and UHP (1.1 eq) in MeCN at 30 ºC after 24 h at 250 rpm.



1k (Y-C-X = CH_2) **2k** **2l**
1l (Y-C-X = C=O)

Entry	Substrate	Enzyme	*c* (%)[a]
1	Limonene (**1k**)	RML	18 (**2k**)
2	(*S*)-Carvone (**1l**)	RML	78 (**2l**)
3	Limonene (**1k**)	CAL-B	20 (**2k**)
4	(*S*)-Carvone (**1l**)	CAL-B	80 (**2l**)

[a] Conversion values into epoxides **2k** or **2l** determined by GC.

3. Conclusions

In summary, a chemoenzymatic approach for the epoxidation of alkenes has been studied using the lipase from *Rhizomucor miehei*. Until now, this enzyme has been scarcely reported in the literature for this type of indirect epoxidation reactions, probably because of the versatility of *Candida antarctica* lipase B. Reaction parameters have been optimized finding adequate conditions for the recovery of a series of epoxides in moderate to excellent yields. Thus, acetonitrile as solvent, lauric acid as peracid precursor and the urea-hydrogen peroxide as oxidant were found to be compatible with the use of RML. Significantly, the selective epoxidation of limonene and (*S*)-carvone were investigated using both RML and CAL-B, finding a complete preference for the oxidation of the exocyclic alkene bond in the case of the (*S*)-carvone and for the internal alkene bond in the case of the limonene demonstrating the potential of enzymes, particularly hydrolases for selective chemoenzymatic transformations.

4. Experimental section

4.1. General considerations.

Rhizomucor miehei lipase (150 U/g) and *Candida antarctica* lipase type B (7600 PLU/g) were a gift from Novozymes. Chemical reagents were purchased from different commercial sources and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. Flash chromatographies were performed using silica gel 60 (230-240 mesh). ^{1}H and ^{13}C NMR experiments were obtained using a Brüker AV-300 spectrometer (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz).

4.2. Analytical conditions for determination of conversion values.

Gas chromatography analyses were carried out in a HP6890 chromatograph with FID detection. Two non chiral columns were used for the identification and quantification of alkenes and epoxides.

A Hewlett Packard HP5 (30 m x 0.32 mm x 0.25 µm) using the following program 30 (°C)/ 3 (min)/ 15 (°C/min)/ 200 (°C)/ 2 (min), was used for **1a** (2.8 min), **2a** (5.4 min), **1b** (4.4 min) and **2b** (6.1 min).

A Hewlett Packard HP1 (30 m x 0.32 mm x 0.25 µm) with the following programs of temperatures:

a) 50 (°C)/ 3 (min)/ 15 (°C/min)/ 200 (°C)/ 3 (min) for **1c** (2.1 min), **2c** (4.4 min), **1f** (2.2 min) and **2f** (4.3 min).

b) 90 (°C)/ 3 (min)/ 15 (°C/min)/ 200 (°C)/ 3 (min) for **1d** (4.0 min), **2d** (6.4 min), **1e** (8.1 min), **2e** (10.0 min), **1h** (3.6 min), **2h** (5.3 min), **1i** (3.8 min), **2i** (5.8 min), **1j** (7.0 min) and **2j** (8.9 min).

c) 70 (°C)/ 3 (min)/ 15 (°C/min)/ 200 (°C)/ 3 (min) for **1g** (2.0 min) and **2g** (4.1 min).

d) 120 (°C)/ 3 (min)/ 15 (°C/min)/ 200 (°C)/ 3 (min) for **1k** (1.9 min), **2k** (3.0 min), **1l** (3.7 min) and **2l** (5.7 min).

4.3. General procedure for the epoxidation of alkenes at 1 mmol scale.

Lauric acid (2 mol, 400 mg), RML (50 mg) and finally UHP (1.1 mmol, 104 mg) were added over a solution of the corresponding alkene **1a**-**h** (1 mmol, 0.66 M) in acetonitrile (1.5 mL). The suspension was shaken at 250 rpm for 24 h at 30 ºC, and then the reaction was quenched by addition of water (1.5 mL). The mixture was extracted with EtOAc (3 x 1.5 mL), and an aliquot of the reaction was injected in the GC for the measurement of the conversion values.

*4.4. General procedure for the epoxidation of 1,4-dihydronaphtalene (**1d**) at 10 mmol scale.*

Lauric acid (20 mmol, 4.01 g), RML (500 mg) and finally UHP (11.1 mmol, 1.04 g) were added over a solution of 1,4-dihydronaphtalene (**1d**, 10 mmol, 0.66 M) in acetonitrile (15 mL). The suspension was stirred for 24 h at 30 ºC. After this time the reaction was quenched by addition of water (15 mL), and the mixture extracted with EtOAc (3 x 15 mL).

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