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Article

Fast Microwave-Assisted Resolution of (±)-Cyanohydrins Promoted by Lipase from *Candida antarctica*

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Enzymatic kinetic resolution (EKR) of (±)-cyanohydrins was performed by using immobilized lipase from *Candida antarctica* (CALB) under conventional ordinary conditions (orbital shaking) and under microwave radiation (MW). The use of microwave radiation contributed very expressively on the reduction of the reaction time from 24 to 2 h. Most importantly, high selectivity (up to 92% ee_p) as well as conversion was achieved under MW radiation (50-56%).

Keywords: CALB, biocatalysis, enzymatic resolution, microwave radiation, cyanohydrins

Introduction

Enantiomerically pure cyanohydrins are important intermediates for the synthesis of organic compounds, such as carboxylic acids and their derivatives, amines and heterocycles as triazoles and tetrazoles.[1-3]

Stereoselective syntheses of cyanohydrins have been investigated by enzymatic methods and have received expressive attention, due to its intrinsic enantio, regio and chemoselectivities.[4-7]

Microwave has proven to be a very important alternative energy source and has become a usual synthetic tool for chemists. One of the most expressive advantages of the microwave-assisted transformations is centered on the reduction of the reaction time, reproducibility and in many cases, pronounced increase of yields in comparison with the transformations carried out under conventional heating.[3,6,8] However, its application for enzymatic-assisted transformations is still almost unexplored.[7,8]

Recently, our group reported the results concerning the esterification of (±)-mandelonitrile with vinyl acetate as acylating agent, in toluene catalyzed by *Candida antarctica* lipase B (CALB) under orbital shaking and under microwave radiation.[6] Aiming to explore more extensively the scope and limitations of such conditions for enzymatic catalyzed asymmetric transformations, in this paper present our results on the enzymatic kinetic resolution of cyanohydrins by CALB under microwave radiation and conventional conditions.

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Experimental

General

The cinnamaldehyde **1a**, 4-chlorobenzaldehyde **1b**, 4-fluorobenzaldehyde **1c**, 4-hydroxybenzaldehyde **1d**, 4-methoxybenzaldehyde **1e**, 3-phenoxybenzaldehyde **1f** and 2-hydroxybutanenitrile **1g** were purchased from Sigma-Aldrich (St. Louis, MO, USA). Sodium borohydride and methanol were purchased from Synth (Diadema, SP, Brazil) and Tedia (Rio de Janeiro, RJ, Brazil), respectively. For gas chromatography-mass spectrometry (GC-MS), a Shimadzu GC2010 Plus gas chromatography system coupled to a mass selective detector (Shimadzu MS2010 Plus, Tokyo, Japan) in electron ionization (70 eV) mode was used. The enzymatic reactions were analyzed in a Shimadzu GC 2010 gas chromatographer equipped with an AOC 20i auto injector, a flame ionization detector (FID), and a chiral column CP-7502 Chiralsil-Dex β (cyclodextrin 25 m × 0.25 mm × 0.39 μm). Fourier transform infrared (FTIR) spectra were recorded on a Bomen MB-100 spectrometer; samples were prepared as thin films on

KBr disks (solid samples) or liquid film (liquid samples) and recorded between 4000-400 cm^{-1}. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Agilent Technologies 500/54 Premium Shielded using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard unless otherwise noted; the chemical shifts are given in ppm and coupling constants (*J*) in Hz.

The enantiomeric excesses (*ee*) of (*R*)-alcohols and (*S*)-acetates were determined by gas chromatography analyses with chiral stationary phase employing the retention times obtained for both enantiomers (±)-**2a**-**g** and (±)-**3a**-**g**. Reagents and solvents were used as obtained commercially and when necessary were purified and/or dried using procedures described in the literature.[9] Column chromatography separations were carried out using silica gel 60 (400-230 mesh) with hexane and ethyl acetate mixtures as eluent. Optical rotations were measured in $CHCl_3$, in a JASCO P2000 polarimeter equipped with a 589 nm Na lamp.

Synthesis of (±)-cyanohydrins **2a**-**g**

The (±)-cyanohydrins **2a**-**g** were synthesized according to the methodology previously established.[3]

To a vial flask (25 mL) was added a mixture of dimethylsulfoxide (DMSO) and H_2O (5 mL, 5:1 v/v), trimethylsilyl cyanide (TMSCN, 0.7 mmol) and the appropriate aldehyde. The reaction mixture was stirred at room temperature for 12 h. After, was added in the reaction mixture HCl solution (10%, 5 mL) and water (10 mL), then extracted with ethyl acetate (3 × 25 mL). The combined organic phases were evaporated under reduced pressure and purified by column chromatography on silica gel using Et_2O/EtOAc (8:2) as eluent, leading to the corresponding products: **2a** (82%), **2b** (81%), **2c** (61%), **2d** (86%), **2e** (45%), **2f** (95%), and **2g** (70%).

Synthesis of (±)-cyanohydrin acetates **3a**-**g**

(±)-Cyanohydrin (**1a**, 0.1 mmol, 0.0118 mL), pyridine (12.4 mmol, 0.997 mL) and acetic anhydride (10.5 mmol, 0.991 mL) were mixed in a 25 mL flask equipped with a magnetic stirrer. The mixture was stirred for 24 h at room temperature. The reaction was stopped by the addition of 10% HCl solution (2 mL) and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and then filtered. The organic solvent was evaporated under reduced pressure yielding the corresponding products: **2a** (86%), **2b** (85%), **2c** (82%), **2d** (70%), **2e** (86%), **2f** (71%) and **2g** (86%). The compounds did not require purification by column chromatography.

Kinetic resolution of (±)-cyanohydrins **2a**-**g** by lipase from *Candida antarctica* under orbital shaking

In a 50 mL vial flask were added toluene (10 mL), vinyl acetate (5.4 mmol, 0.5 mL), *C. antarctica* lipase (160 mg, CALB ≥ 10,000 U g^{-1} protein, expressed in *Aspergillus oryzae* and immobilized on acrylic resin donated by Novo Nordisk, Araucária, PR, Brazil) and the appropriate (±)-cyanohydrin **2a** (0.29 mmol), **2b** (0.23 mmol), **2c** (0.33 mmol), **2d** (0.40 mmol), **2e** (0.29 mmol), **2f** (0.22 mmol) or **2g** (0.45 mmol). The reaction mixtures were incubated in an orbital shaker (130 rpm, at 32 ºC). The progress of the reactions was followed by removing 30 µL-samples of the reaction mixture, which were diluted to 600 µL of EtOAc and analyzed by gas chromatography coupled to a flame ionization detector (GC-FID). After the reaction completion, the lipase was filtered off. The filtrate was evaporated under reduced pressure and the products were purified by column chromatography on silica gel using hexanes and ethyl acetate (8:2) as eluent, yielding the enantiomerically enriched (*R*)-alcohols **2a**-**c**, **2e**-**f** and (*S*)-acetates **3a**-**c**, **3e**-**f**.

Kinetic resolution of (±)-cyanohydrins **2a**-**g** by lipase from *Candida antarctica* under microwave radiation

In a 50 mL vial flask was added toluene (10 mL), vinyl acetate (5.4 mmol, 0.5 mL), *C. antarctica* lipase (160 mg, CALB ≥ 10,000 U g^{-1} protein, expressed in *Aspergillus oryzae* and immobilized on acrylic resin donated by Novo Nordisk, Araucária, PR, Brazil) and the appropriate (±)-cyanohydrin **2a** (0.29 mmol), **2b** (0.23 mmol), **2c** (0.33 mmol), **2d** (0.40 mmol), **2e** (0.29 mmol), **2f** (0.22 mmol) or **2g** (0.45 mmol). The reactions were carried out in CEM Discover Microwave reactor at 65 and 80 ºC (200 W). The progress of the reactions was followed by removing 250 µL-samples of the reaction mixture, which was diluted to 600 µL of EtOAc and analyzed by GC-FID. After reaction completion, the lipase was filtered off. The filtrate was evaporated under reduced pressure and purified by column chromatography on silica gel using hexanes/ethyl acetate (8:2) as eluent, yielding the enantiomerically enriched (*R*)-alcohols **2a**-**c**, **2e**-**f** and (*S*)-acetates **3a**-**c**, **3e**-**f**.

Derivatization of unreacted alcohols

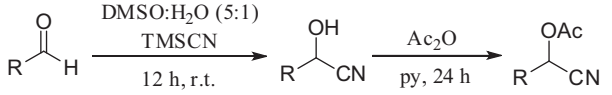
The alcohols not esterified by CALB were added to a test tube [**2a** (0.22 mmol), **2b** (0.18 mmol), **2e** (0.22 mmol), **2f** (0.16 mmol) and **2g** (2.19 mmol)] followed by pyridine (6.2 mmol) and acetic anhydride (5.2 mmol) then submitted to magnetic stirring for 24 h. After that, two drops of a 10%

HCl solution were added to each test tube. Water (10 mL) was added, followed by extraction with ethyl acetate (3 × 3 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. Subsequently, samples were diluted in ethyl acetate in vials and analyzed to determine the enantiomeric excesses by GC-FID analysis.

Enantioseparation on chiral column was performed on a CP-7502 CP-Chirasil-Dex CB, 25 m × 0.25 mm × 0.39 μm. Alcohols presented the following retention times: (*R*-**2a**, 8.77 min; *S*-**2a**, 8.77 min), (*R*-**2b**, 5.74 min; *S*-**2b**, 5.74 min), (*S*-**2c**, 20.57 min; *R*-**2c**, 20.77 min), (*R*-**2d**, 14.68 min; *S*-**2d**, 14.68 min), (*R*-**2e**, 16.18 min; *S*-**2e**, 16.18 min), (*R*-**2f**, 14.14 min; *S*-**2f**, 14.14 min), (*R*-**2g**, 16.49 min; *S*-**2g**, 16.49 min), alcohols **2a**-**b** and **2d**-**f** had no enantioseparation. Retention times for the acetates: (*R*-**3a**, 20.35 min; *S*-**3a**, 21.68 min), (*R*-**3b**, 12.82 min; *S*-**3b**, 13.47 min), (*R*-**3c**, 9.28 min; *S*-**3c**, 10.97 min), (*R*-**3d**, 17.20 min; *S*-**3d**, 17.65 min), (*R*-**3e**, 29.31 min; *S*-**3e**, 30.95 min), (*R*-**3f**, 27.09 min; *S*-**3f**, 27.96 min), (*R*-**3g**, 10.26 min; *S*-**3e**, 12.29 min). For experimental conditions of the GC-FID analysis see Supplementary Information.

Results and Discussion

The racemic cyanohydrins **2a**-**g** and their corresponding acetates (**3a**-**g**) were prepared in reasonable to good yields according to standard conditions (Scheme 1).[3,6]



R = PhCHCH (**1a**)	**2a** (82%)	**3a** (86%)
R = *p*-Cl-Ph (**1b**)	**2b** (81%)	**3b** (85%)
R = *p*-F-Ph (**1c**)	**2c** (61%)	**3c** (82%)
R = *p*-OH-Ph (**1b**)	**2d** (86%)	**3d** (70%)
R = *p*-MeO-Ph (**1e**)	**2e** (45%)	**3e** (86%)
R = 3-PhO-Ph (**1f**)	**2f** (95%)	**3f** (71%)
R = Et (**1g**)	**2g** (70%)	**3g** (86%)

Scheme 1. Syntheses of (±)-cyanohydrins **2a**-**g** and the corresponding acetates **3a**-**g**.

The activity, as well as the enantioselectivity, in enzymatic kinetic resolution reactions are strongly influenced by the reaction conditions, including solvent, concentration and temperature, being the latter parameter one of the most critical.[6-11] Having this information in mind, we decided to investigate the enzymatic kinetic resolution using *Candida antarctica* as biocatalyst of (±)-cyanohydrins (**2a**-**g**), comparatively, under conventional (orbital shaking) and microwave-assisted conditions. Results are summarized in Tables 1 and 2.

Enzymatic kinetic resolution (EKR) of (±)-cyanohydrins (**2a**-**g**) under orbital shaking

The reaction of (±)-**2a**, under reaction conditions presented in Table 1, resulted in the desired acylated product (*S*)-**3a** in good conversion and reasonable selectivity (c = 57%, 87% ee_p) (entry 1, Table 1). Compounds (±)-**2b** and (±)-**2c**, both possessing electron-withdrawing substituents at the *para* position, presented virtually the same behavior with good conversions and high enantioselectivities (96% ee_p and 97% ee_p, respectively - entries 2 and 3, Table 1). Higher reaction time was necessary to achieve just reasonable conversion (32%) and poor enantioselectivity (28% ee_p) when (±)-cyanohydrin **2d**, bearing an electron-donating group at the *para* position, was submitted to the same reaction conditions (entry 4, Table 1). On the other hand, a *p*-OMe-substituted substrate, also an electron-rich substituent (entry 5, Table 1), presented similar results to those observed for the examples of entries 2 and 3, containing electron-withdrawing substituents. Compound (±)-**2f**, the only example bearing a *meta*-substituent, also presented practically the same conversion (47%) and selectivity (92% ee_p) averages as most compounds discussed before. The only alkyl cyanohydrin **2g** submitted to the study presented very poor results, suggesting that the low selectivity is a consequence of the low steric volume of the alkyl chain, which is in accordance with enzymatic resolutions (entry 7, Table 1).

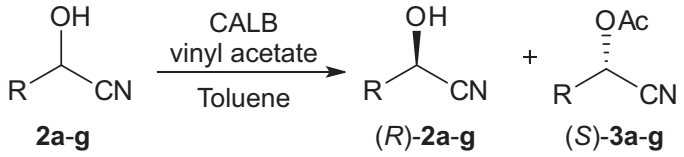
The low conversion observed for cyanohydrin **2d** can be attributed to its instability under the reaction conditions. The reaction performance was monitored by GC-MS analysis and beyond the expected unreacted substrate (**2d**) and the acetylated product **3d**, there was also identified the aldehyde precursor of the cyanoydrin, what is a result of the thermic cleavage of the substrate.[6,13]

The substrates were also submitted to the enzymatic kinetic resolution, under similar reaction condition, instead to the fact that the energy source was supplied by a microwave oven and the results are summarized in Table 2.

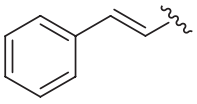
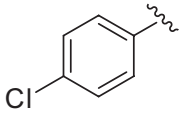
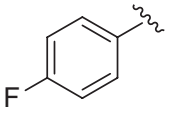
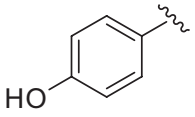
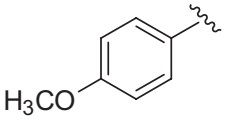
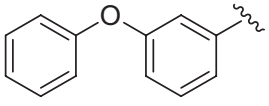
Enzymatic kinetic resolution of (±)-cyanohydrins (**2a**-**f**) under microwave radiation

It is well known that microwave radiation is frequently associated with improving reaction performances, accelerating organic transformations in comparison with conventional heating, which is due to the higher efficiency of the energy transfer process to the reaction media.[6,13] In our experiments, in a general sense, the reaction time under microwave radiation was deeply decreased to just

Table 1. Enzymatic kinetic resolution of (±)-cyanohydrins (**2a**-**g**) using vinyl acetate as acylating agent in toluene, catalyzed by CALB under orbital shaking (32 °C, 130 rpm)



2a-g (*R*)-**2a-g** (*S*)-**3a-g**

		Orbital shaking				
entry	R	time / h	c[a] / %	ee_p[b] / %	ac	*E*[c]
1	 **2a**	24	57(39)[d]	87	*S*	28
2	 **2b**	24	55	96	*S*	nd
3	 **2c**	24	55	97	*S*	> 200
4	 **2d**	48	32	28	*S*	nd
5	 **2e**	24	56	99	*S*	nd
6	 **2f**	24	47	92	*S*	nd
7	 **2g**	48	18	25	*S*	nd

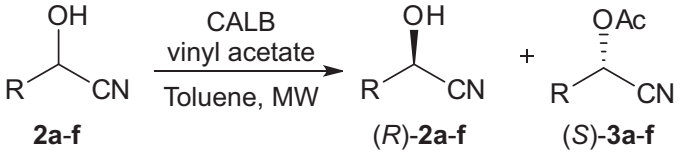
[a]Conversion: $c = ee_s / (ee_s + ee_p)$;[12] [b]CG-FID = $ee_s / (ee_p + ee_s)$;[12] [c]$E = \ln[ee_p(1 - ee_s) / (ee_p + ee_s)] / \ln[ee_p(1 + ee_s) / (ee_p + ee_s)]$;[12] [d]isolated yields after colum chromatography. ac: Absolute configuration; nd: not determined.

few hours (2-6) resulting in selectivity and conversions of the same average as those of the conventional conditions. In only 2 h cyanohydrin **2a** was efficiently converted to the corresponding acetate (*S*)-**3a** (52%) in moderate selectivity (79% ee_p, entry 1, Table 2).

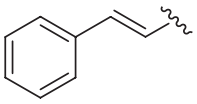
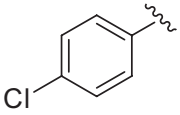
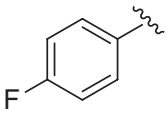
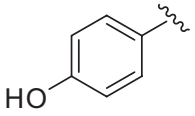
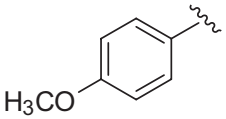
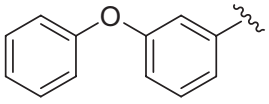
Compounds (±)-**2b** and (±)-**2c** yielded the acetylated products in good conversions (c = 53% and 50%, respectively) and selectivities (90% and 92% ee_p, respectively) (entries 2 and 3, Table 2). As observed for the study carried out under orbital shaking at 32 °C, the reaction with **2d** proceeded poorly presenting very low conversion and optical purity (entry 4, Table 2).

Kinetic resolution of (±)-**2e** was achieved after 3 h under microwave radiation to give (*S*)-**3e** with good conversion and enantioselectivity (c = 56%, 90% ee_p, entry 5, Table 2). For (±)-**2f** it was possible to obtain (*S*)-**3f** with good conversion and moderate selectivity (c = 50%, 84% ee_p, entry 6, Table 2).

Table 2. Enzymatic resolution of (±)-cyanohydrins (**2a**-**f**) with vinyl acetate in toluene catalyzed by CALB under microwave radiation (80 °C, 200 W)



2a-f (*R*)-**2a-f** (*S*)-**3a-f**

Microwave radiation						
entry	R	time / h	c[a] / %	ee_p[b] / %	ac	*E*[c]
1	 **2a**	2	52	79	*S*	nd
2	 **2b**[e]	5	53 (30)[d]	90	*S*	48
3	 **2c**	4	50 (65)[d]	92	*S*	70
4	 **2d**	5	17	59	*S*	nd
5	 **2e**	3	56 (70)[d]	90	*S*	41
6	 **2f**	6	50 (83)[d]	84	*S*	30

[a]Conversion: $c = ee_s / (ee_s + ee_p)$;[12] [b]CG-FID = $ee_s / (ee_p + ee_s)$;[12] [c]$E = \ln[ee_p(1 - ee_s) / (ee_p + ee_s)] / \ln[ee_p(1 + ee_s) / (ee_p + ee_s)]$;[12] [d]isolated yields after chromatographic column purification; [e](65 °C, 200 W). ac: Absolute configuration; nd: not determined.

Absolute configuration of the acetates (**3a**-**g**) was assigned as *S* configuration by comparison with optical rotation values described in the literature (Table 3). Consequently, it was possible to observe that the immobilized lipase has stereochemical preference for *S*-acetate esterification. Thus, the observed esterification preference is in agreement with the predictions of the Kazlauskas rule.[15-22]

Recently, we described the highly enantioselective acylation of chlorohydrins using Amano AK lipase from Pseudomonas fluorescens immobilized on silk fibroin–alginate spheres.[23]

Enzyme recyclability studies

To examine the stability of the enzyme under the microwave-assisted reaction conditions, cyanohydrin **2a** was selected as model compound for the recyclability resolution reaction. After each reaction, the catalyst was isolated by filtration, washed with ethyl acetate, dried

Table 3. Optical rotations of the cyanohydrins **2a**-**g** and acetates **3a**-**g** obtained by kinetic resolution using CALB

Compound	$[\alpha]_D^T$ Experimental	$[\alpha]_D^T$ Literature
(*R*)-**2a**	$[\alpha]_D^{24}$ –11.0 (*c* 0.012, $CHCl_3$, 91% ee_s)	$[\alpha]_D^{25}$ –28.1 (*c* 0.12, C_6H_6, 87% ee_s)[14]
(*R*)-**2b**	$[\alpha]_D^{26}$ –2.6 (*c* 0.016, $CHCl_3$, >99% ee_s)	$[\alpha]_D^{26}$ –24.2 (*c* 0.12, C_6H_6, 73% ee_s)[14]
(*R*)-**2c**	$[\alpha]_D^{23}$ +21.4 (*c* 0.21, $CHCl_3$, 88% ee_s)	$[\alpha]_D^{25}$ +23.5 (*c* 0.26, $CHCl_3$, 71% ee_s)[14]
(*R*)-**2d**	nd	–
(*R*)-**2e**	$[\alpha]_D^{23}$ +0.020 (*c* 0.005, $CHCl_3$, 73% ee_s)	$[\alpha]_D^{20}$ +9.8 (*c* 1.22, $CHCl_3$, 19% ee_s)[15]
(*R*)-**2f**	$[\alpha]_D^{23}$ +0.020 (*c* 0.005, $CHCl_3$, 73% ee_s)	$[\alpha]_D^{25}$ +12.9 (*c* 1.0, $CHCl_3$, 78% ee_s)[16]
(*R*)-**2g**	nd	–
(*S*)-**3a**	$[\alpha]_D^{24}$ +37.41 (*c* 0.015, $CHCl_3$, 79% ee_p)	$[\alpha]_D^{25}$ +14.4 (*c* 0.011, $CHCl_3$, > 99% ee_p)[17]
(*S*)-**3b**	$[\alpha]_D^{26}$ +3.90 (*c* 0.011, $CHCl_3$, 90% ee_p)	$[\alpha]_D^{20}$ +6.90 (*c* 0.80, $CHCl_3$, 65.5% ee_p)[18]
(*S*)-**3c**	$[\alpha]_D^{23}$ –6.7 (*c* 0.012, $CHCl_3$, 92% ee_p)	$[\alpha]_D^{26}$ –1.98 (*c* 1.01, $CHCl_3$, 82% ee_p)[19]
(*S*)-**3d**	nd	–
(*S*)-**3e**	$[\alpha]_D^{23}$ –0.08 (*c* 0.015, $CHCl_3$, 90% ee_p)	$[\alpha]_D^{24}$ –3.1 (*c* 1.10, CH_2Cl_2, 71% ee_p)[20]
(*S*)-**3f**	$[\alpha]_D^{23}$ –0.08 (*c* 0.015, $CHCl_3$, 84% ee_p)	$[\alpha]_D^{20}$ –7.02 (*c* 0.01, $CHCl_3$, 99% ee_p)[14]
(*S*)-**3g**	nd	–

nd: Not determined.

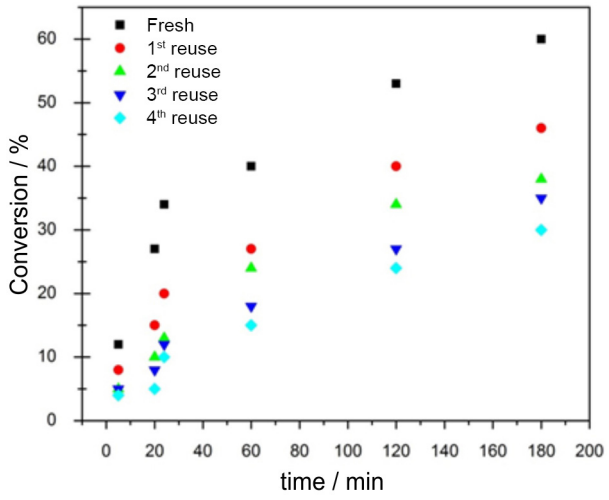


Figure. 1. Effect of recyclability of the biocatalyst under microwave radiation (200 W, 300 rpm). Experiments were conducted in toluene (10 mL), **2a** (0.3 mmol) and CALB (160 mg).

at room temperature and submitted to the next reaction cycle. Constant conversion decrease was observed in each cycle as can be visualized in the graph in Figure 1. Longer reaction times were also necessary to achieve high conversions. Even being compromised, the activity of the enzyme was reasonably maintained, opening opportunities for recyclability of the biocatalyst for preparative purposes, which is quite attractive in the industrial point of view, considering the high price of this catalyst.

Conclusions

In summary, we demonstrated that microwave radiation can be useful also for enzymatic-assisted transformations. Albeit not extraordinary, good conversions and selectivities were achieved and more importantly, the required reaction time was deeply diminished for all studied cases leading to the corresponding desired compounds in reasonable good optical enrichments. The reutilization of the catalyst was possible demonstrating that the activity of the enzyme was not completely lost under the microwave conditions, which is quite attractive considering the price of the catalyst.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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