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Diastereoselective and enantioselective alkaline-hydrolysis of 2-aryl-1-cyclohexyl acetate: a CAL-B catalyzed deacylation/acylation tandem process

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ABSTRACT

Candida antarctica lipase proved to be a particularly efficient lipase for the resolution of racemic 2-aryl-cyclohexyl acetate in hydrolysis reaction with Na_2CO_3 in an organic medium. The (1*R*,2*S*)-*trans*-2-arylcyclohexanols **2a**–**2d** were obtained with high ee values (up to >99%) and the selectivity reached $E > 200$. The influence of the enol ester and the solvent on (±)-*trans*-2-arylcyclohexanol in the CAL-B catalyzed acylation was also studied and compared with the deacylation. The CAL-B exhibits a better affinity for the alkaline hydrolysis reaction compared with acylation with the enol esters in the same organic solvents. The best conditions were applied to resolve a stereoisomeric mixture *cis*/*trans*-2-phenyl-1-cyclohexanol and its corresponding acetate by acylation and deacylation. The obtained results show a highly enantio- and diastereoselectivity of the CAL-B during the acylation and the deacylation in favor of the *trans*-(*R*)-enantiomer product. The resolution of a mixture of *cis*/*trans*-2-arylcyclohexanols was an easy, convenient approach to provide only one stereoisomer of a mixture of four with high enantiomeric excess.

1. Introduction

The importance of enantiopure secondary alcohols derivatives as versatile building blocks for the synthesis of biologically active compounds is well established.[1] The *trans*-2-arylcyclohexanol derivatives, developed by Whitesell et al.,[2] are important as chiral sources for asymmetric transformations or chiral materials for the asymmetric manufacture of physiologically active substances such as diltiazem.[3] Their high asymmetric inductions are attributed to the high stereoselective control due to both steric and electronic effects of the aryl moiety. The routes reported in the literature to access enantioenriched *trans*-2-phenylcyclohexanol use asymmetric transformations such as hydroboration,[4] epoxidation[5] or dihydroxylation[6] of 1-phenylcyclohexene, or also by enantioselective protonation/reduction starting from the corresponding prochiral enol acetate.[7] Other routes have also used kinetic resolutions[8] such as the diastereo- and enantioselective silylation of 2-arylcyclohexanols.[9] The enzymatic acylation of the *rac*-*trans*-2-arylcyclohexanols has been used as an easy route with various lipases: *Pseudomonas amano* sp.,[10] *PS30* lipase,[11] *Candida rugosa* lipase (*CRL*)[12] and *Pseudomonas fluorescens* lipase (AK).[13] The standard protocol reported for these reactions engages vinyl acetate as acyl donor and *tert*-butylmethylether (TBME) as solvent. The enzymatic hydrolysis of *trans*-2-arylcyclohexyl derivatives is less reported, to the best of our knowledge, with only the *Crude Chicken Liver* Esterase (*CCLE*) being used in biphasic media.[14] The lipase from *Candida antarctica* fraction B is a very robust biocatalyst in an organic medium, with high catalytic efficiency in kinetic resolutions.[15] In our previous work, CAL-B was successfully used for the resolution of arylakylcarbinols[16] and primary 1,2-disbstituted ferrocene derivatives.[17] Furthermore, we have developed a green and easy pathway for the enzymatic hydrolysis in non-aqueous organic media, in the presence of sodium carbonates.[18] We have also effectively applied this procedure to the deracemization of a large range of aromatic acetates[19] and the chemoselective deacylation of *N*,*O*-protected amino alcohols.[20]

In order to extend the field of application of the CAL-B catalyzed alkaline hydrolysis approach, we applied it to some *trans*-2-arylcyclohexyl derivatives. Herein we describe the kinetic resolution via alkaline hydrolysis mediated by CAL-B of four compounds:

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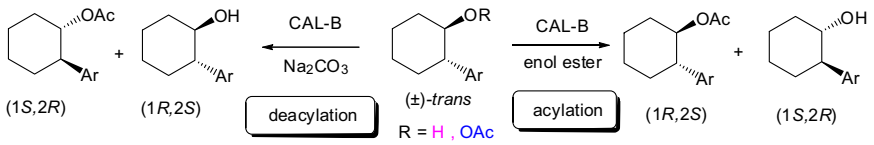
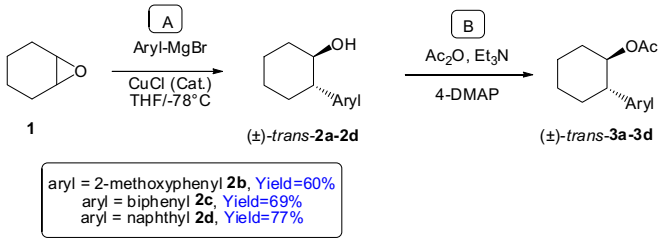


Scheme 1. Acylation/deacylation tandem approaches.

trans-2-phenyl-cyclohexyl acetate **3a**, *trans*-2(2-methoxyphenyl)-cyclohexyl acetate **3b**, *trans*-([1,1′-biphenyl]-4-yl)-cyclohexyl acetate **3c**, *trans*-2-(naphthalen-2-yl)-cyclohexyl acetate **3d**. The efficiency of CAL-B as a biocatalyst used in the alkaline hydrolysis approach is comparable to the acylation reaction using two different enol esters in various solvents (Scheme 1). We also studied the isomeric mixture of *cis*–*trans*-2-phenyl-1-cyclohexanol. The optimized conditions of both approaches are applied to the direct diastereo- and enantioselective resolution of racemic *cis*–*trans*-2-phenyl-1-cyclohexanol.

2. Results and discussion

Herein we focused on four substrates: (±)-*trans*-2-arylcyclohexyl derivatives **2a**–**2d** and **3a**–**3** including aryl groups with different steric and electronic environments. The first one (±)-*trans*-2-phenyl-1-cyclohexanol **2a** is commercially available, while the last three **2b**, **2c**, **2d** are obtained via copper(I) catalyzed ring opening of cyclohexane oxide **1** by means of the appropriate arylmagnesium bromide with satisfactory yields (Scheme 2A). The (±)-*trans*-2-arylcyclohexyl acetates **3a**–**3d** were obtained via standard chemical acylation (Scheme 2B).

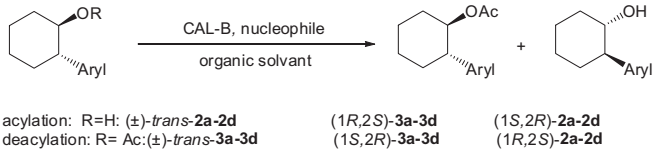


Scheme 2. Synthesis of *trans*-2-arylcyclohexyl derivatives.

The *Candida antarctica* lipase fraction B, immobilized on acrylic resin, was used as the catalyst for the kinetic resolution of acetates **3a**–**3d** via alkaline hydrolysis. The same lipase was used for the acylation of alcohols **2a**–**2d** by two enol esters in organic solvents with different hydrophobicities, the *tert*-butylmethylether (TBME, log*P* = 1.35) and toluene (PhMe, log*P* = 2.5).

2.1. CAL-B catalyzed deacylation/ acylation of (±)-*trans*-2-Arylcyclohexyl derivatives

The alkaline hydrolysis experiments are established on an equimolecular mixture of racemic acetates **3a**–**3d** and sodium carbonate (1 mmol/1 mmol), diluted in 2 mL of organic solvent, in the presence 200 mg of CAL-B (>10,000 U/g). The acylation experiments were performed on 1 mmol of racemic alcohols **2a**–**2d** with 3 equiv of enol esters:vinyl acetate (VA) and isopropenyl acetate in 2 mL of organic solvent with the same loading amount of CAL-B. The reaction mixture of the alkaline hydrolysis was stirred at 40 °C for three days and that of the acylation was stirred for one day at room temperature. The isolated yields of the products and the residual substrates were quantified after removing the lipase by simple filtration and their separation by flash chromatography. Their enantiomeric excesses were determined by chiral HPLC or GC



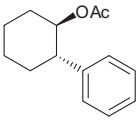
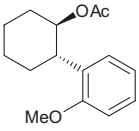
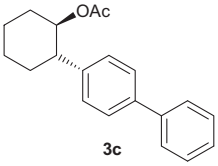
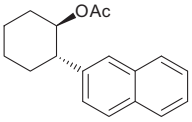
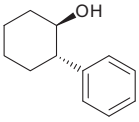
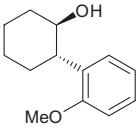
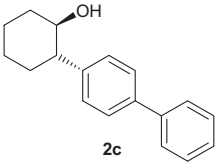
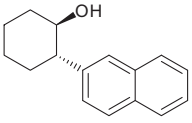
Scheme 3. Enzymatic deacylation/acylation approaches of *trans*-2-arylcyclohexyl derivatives.

(Scheme 3). The stereochemical preference of the CAL-B was determined by establishing the absolute configuration of the remaining alcohols and acetates after comparison of the specific rotations with those reported in the literature. In both cases CAL-B preferentially catalyzed the (1*R*)-enantiomer following Kazlauskas rule.[21] The results of both enzymatic resolution approaches of *rac*-*trans*-2-arylcyclohexyl derivatives are summarized in Table 1.

All the experiments show a high enantioselectivity of the CAL-B during the alkaline hydrolysis of acetates **3a**–**3d** (Table 1). The conversions essentially depend on both the bulkiness of the aryl substituent and the solvent hydrophobicity. The best results are recorded using TBME as the solvent in deacylation where the CAL-B hydrolyze efficiently the acetates **3a** and **3c** in favor of the (1*R*,2*S*)-enantiomer (entries 2 and 5). Moderate conversions are noted in toluene for **3a** and **3b** $17\% \leq c \leq 30\%$ (entries 1 and 3). In TBME as solvent, a conversion of 46.5% was reached for **3a**, while the conversion strongly decreases in the case of more hindered and less soluble substrate **3b** (entry 2 and 4); the same effect being noted in toluene (entry 3 vs. 1). Based on those results, the hydrolysis reactions of **3c** and **3d** are performed only in TBME. The recorded results are in the same lines, the acetates **3c** and **3d** are hydrolyzed selectively ($E > 200$) with conversion rates of $c = 49.5\%$ for **3c** and $c = 31\%$ for **3d** (entries 5 and 6).

Using the same guidelines, the resolution of (±)-*trans*-2-arylcyclohexanol **2a**–**2d** was carried through CAL-B catalyzed acylation using both enol esters and the two solvents used in alkaline hydrolysis. In all cases, high selectivity for the acylation was observed with vinyl and isopropenyl acetates ($E > 97$) in both solvents always with a (*R*)-enantiopreference. However, the CAL-B reactivity was modulated according to the reaction partners: the steric effects of the aryl-substituent's, the enol ester used as well as the solvent. Thus, the presence of either a phenyl or naphthyl substituent contributes in favor of the CAL-B acylation reactivity, and the best results were obtained ($c = 47\%$) using isopropenyl acetate as acyl donor in toluene for **2a** or in TBME with **2d** (entries 7–10 and 19–22). Moreover, isopropenyl acetate shows a significant effect of the solvent for the resolution of **2b**, as the conversion jump from $c = 6\%$ in TBME to $c = 30\%$ in toluene (entry 11 vs. 12). This solvent effect is not observed in the case of the substrates **2a** and **2d** under the same conditions (entries 7–8, and 19–20) while for **2c,** the activity of CAL-B is low $c < 11\%$ (entries 15–16). Furthermore, the presence of a methoxy-substituent at the *ortho*-position of the aromatic ring causes a significant decrease in the conversion using isopropenyl acetate in TBME (entry 11 *vs* 7); this fact is less pronounced in toluene (entry 12 *vs* 8). The same moderate activity of CAL-B lipase occurs during the alkaline hydrolysis of the acetate **3b**.

Table 1
CAL-B catalyzed deacylation of **3a–3d** versus acylation of **2a–2d**

Entry	Substrate	Nucleophile	Solvent	ee_S[c] (%) Yield[d] (%)	ee_P[c] % Yield[d] (%)	C[c] (%)	E[c]
1	 **3a**		Toluene	43 (65)	>99 (24)	30	>200
2			TBME	86 (51)	>99 (38)	46.5	>200
3	 **3b**		Toluene	20 (ND)	99 (ND)	17	>200
4			TBME	38 (68)	>96 (20)	28.4	71
5	 **3c**	Na_2CO_3[a]	TBME	96.5 (45)	>99 (44)	49.5	>200
6	 **3d**		TBME	44 (55)	>99 (25)	31	>200
7	 **2a**	Isopropenyl acetate[b]	TBME	60 (50)	>99 (30)	38	>200
8			Toluene	89 (43)	>99 (40)	47	>200
9		Vinyl acetate[b]	TBME	53.5 (60)	>99 (33)	35	>200
10			Toluene	36.5 (70)	>99 (20)	27	>200
11	 **2b**	Isopropenyl acetate[b]	TBME	6 (ND)	>99 (ND)	6	>200
12			Toluene	42 (55)	>99 (20)	30	>200
13		Vinyl acetate[b]	TBME	32 (ND)	>99 (ND)	25	>200
14			Toluene	6 (ND)	>99 (ND)	6	>200
15	 **2c**	Isopropenyl acetate[b]	TBME	12 (ND)	98 (ND)	11	97
16			Toluene	6 (ND)	98 (ND)	6	>200
17		Vinyl acetate[b]	TBME	24 (69)	>99 (15)	19.5	>200
18			Toluene	5 (ND)	>99 (ND)	5	>200
19	 **2d**	Isopropenyl acetate[b]	TBME	87 (40)	>99 (41)	47	>200
20			Toluene	73 (37)	>99 (40)	42	>200
21		Vinyl acetate[b]	TBME	67 (40)	>99 (32)	40	>200
22			Toluene	38 (65)	>99 (15)	28	>200

ND: No determined.
[a] Reaction conditions: 1 mmol of racemic acetate, 1 mmol of Na_2CO_3, 200 mg of CAL-B, in 2 mL of organic solvent at 40 °C for 72 h.
[b] Reaction conditions: 1 mmol of racemic alcohol, 3 mmol of enol ester, 200 mg of CAL-B, in 2 mL of organic solvent at room temperature for 24 h.
[c] Conversion: $C = ee_S/ee_P + ee_S$; Selectivity: $E = Ln[(1 - C)(1 - ee(S))]/Ln[(1 - C)(1 + ee(_S))]$.[22]
[d] Isolated yield after separation by flash chromatography.

When the vinyl acetate was employed as the acyl donor, these results were inverted. In TBME, the conversion was slightly diminished from $c = 35\%$ to $c = 25\%$ (entries 9 and 13), while it was strongly reduced in toluene from $c = 27\%$ to $c = 6\%$ (entries 10 and 14). The use of vinyl acetate as the acyl donor in TBME gave the best CAL-B activity in the acylation of the four substituted-cyclic alcohols $19.5\% \leq C \leq 40\%$ (entries 9, 13, 17 and 21). A drastic decrease of the lipase activity was observed during the acylation of **2c**, and the best conversion $c = 19.5\%$ was obtained using the vinyl acetate in TBME (entry 17). The effect of the structure of the aryl-substituent appeared more clearly in the acylation of **2d**. The lipase CAL-B was still active and selective with a naphthyl group (entries 19–22); the high E value indicates that the spatial structure of substrate **2d** fits nicely in the active site of the enzyme for acylation. This is not the case for substrate **2c**, where the presence of a biphenyl moiety strongly reduces the reactivity of the lipase (entries 15–18). The biphenyl group would undergo steric interactions related to the substituted phenyl, which probably

interferes with the active conformation of the lipase. Similar observations were previously described by the *Pseudomonas fluorescens* lipase with arylalkycarbinols.[23] The impact of the steric effect completely declined during the alkaline hydrolysis, where the recorded conversions for **3c** and **3d** are $c = 49.5\%$ and $c = 31\%$, respectively (entries 5–6). Such results highlight the steric and the spatial requirements for both the reactivity and selectivity of the CAL-B catalyzed acylation of substituted cyclohexanol.

Herein, we have compared two kinetic resolution approaches for *rac*-2-arylcyclohexanols of different structures in an organic medium with CAL-B: the alkaline hydrolysis by Na_2CO_3 and the acylation using two enol esters. The structure and the electronic effects of the aryl-substituent strongly impact both the reactivity and selectivity of the CAL-B and they mutually with the nucleophile used according to the solvent hydrophobicity. The alkaline hydrolysis by means of CAL-B as a biocatalyst constitutes a practical route for the separation of both antipodes of those chiral auxiliaries. Both enzymatic studied approaches are enantiocomplementary with (*R*)-enantioselection of the substrate. Based on the obtained results from the CAL-B catalyzed kinetic resolution of the *trans*-substituted cyclohexanols via alkaline hydrolysis and acylation, the best results were applied to the direct resolution of the racemic isomeric mixture *cis*/*trans*-2-phenyl-1-cyclohexanol.

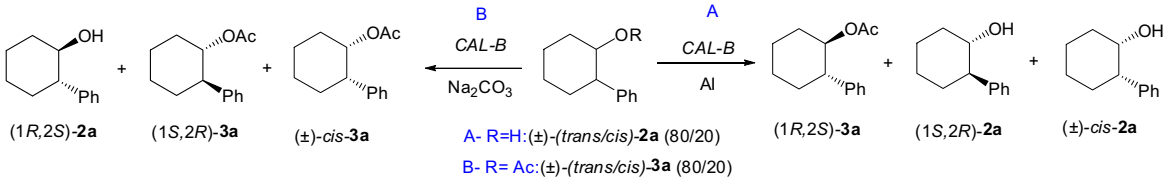
2.2. CAL-B catalyzed Acylation/Deacylation of (±)-*cis*/*trans*-2-phenyl-1-cyclohexanol

To the best of our knowledge, the direct kinetic resolution of the isomeric *cis*/*trans* mixture of 2-phenyl-1-cyclohexanol and derivatives is very modestly reported.[24] At this stage of our investigation, we applied the optimized conditions for the kinetic resolution of the racemic *cis*/*trans*-2-phenyl-1-cyclohexanol in order to examine the CAL-B enantio- and diastereoselectivity during the approaches, alkaline hydrolysis and acylation with enols esters. The isomeric mixture (±)-*cis*/*trans*-2-pheny-1-cyclohexanol **2a** was obtained via reduction of the corresponding ketone using $NaBH_4$ in THF/water, with a diastereoisomeric ratio of *cis*/*trans*: 20/80 (Scheme 4A). The corresponding acetate mixture was prepared via standard chemical acylation (Scheme 4B). The separation of all eight isomers of both *cis*/*trans*-alcohol et *cis*/*trans*-acetate was performed by chiral CG analysis (Fig. 1).

The enzymatic acylation was performed using isopropenyl acetate as the acyl donor in toluene at room temperature, and monitored by chiral GC. Aliquots from the reaction mixture at 24 h, 48 h and 72 h were analyzed. The enzymatic alkaline hydrolysis was carried out in TBME and stirred for 72 hours at 40 °C. The obtained results are given in Table 2.

The CAL-B catalyzed acylation and deacylation was performed and showed that only the *trans*-stereoisomer was transformed, with (*R*)-enantioselection and high E-values achieved ($E > 200$, Table 2). The *cis*-stereoisomer remained untransformed due to its spatial structure, which disadvantages the approach to the active site of CAL-B. Similar observations have been reported during the acylation of *cis*-β-hydroxy-cyclohexanol catalyzed by the CAL-B[24a] and during the acylation of *cis*-4-*tert*-butyl-c-2-ethynyl-r-1-cyclohexanol catalyzed by *PSL*. The study explains that the *cis*-isomer reacts more slowly than the *trans*-analogue by conformational effects on the lipase, which affect both the reactivity and enantioselectivity of this lipase depending on the equatorial or axial position of OH and the bulkiness of the substituent at the 2-position.[25]

In our case, the acylation of *cis*/*trans*-***2a*** using CAL-B showed a high selectivity ($E > 200$), and a conversion of $C = 48\%$ after 72 h of stirring was achieved (entry 3); and the *trans*-(1*R*,2*S*)-**3a** was obtained with ee >99%. The reaction time was prolonged compared to the acylation of the stereoisomer *trans*-**2a** where the same conversion was achieved after 24 h under identical conditions (Table 1: entry 8). Otherwise, the CAL-B maintains a high selectivity during



Scheme 4. Enzymatic deacylation versus acylation of isomeric mixture of *cis*/*trans* (±)-2-phenyl-1-cyclohexyl derivatives.

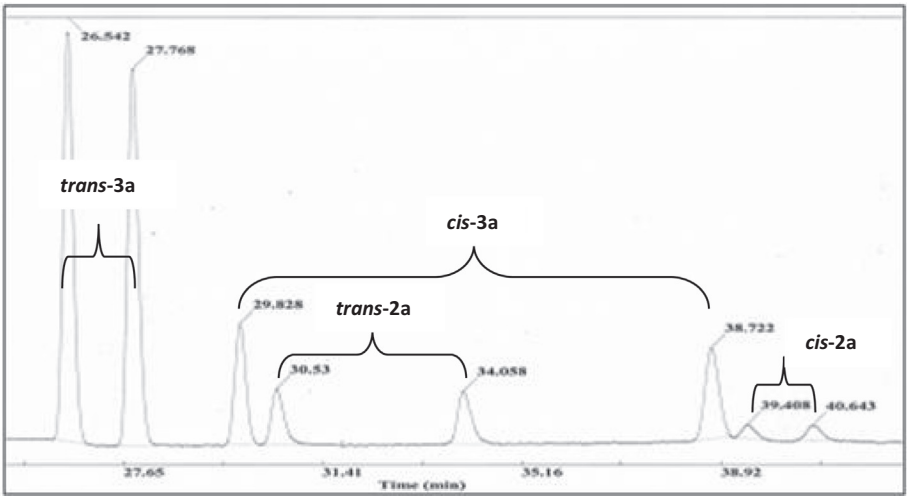


Figure 1. Chromatogram of the isomeric mixtures *cis*/*trans* **2a** and **3a**.

Table 2
CAL-B catalyzed acylation/deacylation of isomeric mixture (±)-*cis*/*trans*-2-phenyl-1-cyclohexyl derivatives

Entry	Approach	Solvent	ee_S[e] (%)	ee_P[e] %	*C*[f] (%)	*E*[f]
1[a]	Acylation	Toluene	58	99	37	>200
2[b]			71	99	42	>200
3[c]			**93**	**99**	**48**	**>200**
4[d]	Deacylation	TBME	**57**	**99**	**36**	**>200**

[a] Reaction conditions: 1 mmol of racemic alcohol, 3 mmol of isopropenyl acetate, 200 mg of CAL-B, in 2 mL of toluene at room temperature for 24 h.
[b] Reaction conditions: for 48 h.
[c] Reaction conditions: for 72 h.
[d] Reaction conditions: 1 mmol of racemic acetate, 1 mmol of Na_2CO_3, 200 mg of CAL-B, in 2 mL of organic solvent at 40 °C for 72 h.
[e] Enantiomeric excess are measured by chiral GC or chiral HPLC.
[f] Conversion: $C = ee_S/ee_P + ee_s$; Selectivity: $E = Ln[(1 - C)(1 - ee_{(S)})]/Ln[(1 - C)(1 + ee_{(S)})]$.[22]

the alkaline hydrolysis of the *cis*/*trans*-**3a** (*E* > 200) and the conversion achieves the threshold of *C* = 36% after 72 h, in favor of *trans*-(1*R*,2*S*)-**2a** with ee >99% (entry 4). For the same reaction time, a conversion of *c* = 46% was recorded during the hydrolysis of *trans*-**2a**-isomer (Table 1: entry 2). The CAL-B catalyzed kinetic resolutions of the isomeric mixtures of either *cis*/*trans*-**2a** or *cis*/*trans*-**3a** are also slowed down. Finally, the kinetic resolution of the isomeric mixture of (±)-*cis*/*trans*-**2a** and (±)-*cis*/*trans*-**3a** by means of CAL-B was enantio- and diastereoselective using the both tandem process: alkaline hydrolysis/acylation.

3. Conclusion

A novel hydrolysis process in TBME with sodium carbonate catalyzed by CAL-B has been successfully extended to a set of *trans*-2-arylcyclohexanols derivatives. The performance of this reaction was improved with various types of *trans*-2-phenylcyclohexanol and this allows direct access to a number of interesting chiral auxiliary with high ee values (up to >99%) and high selectivities *E* > 200, allowing us to isolate enantiomerically pure alcohols and acetates.

The effectiveness of CAL-B in alkaline hydrolysis was compared to acylation with two enol esters in the same solvents. The CAL-B exhibited a better affinity for the alkaline hydrolysis reaction compared with acylation with the enol esters in the same organic solvents. The structure of the aryl group had a significant influence on both the reactivity of the CAL-B lipase. The substitution of the aromatic ring with a methoxy moiety at the *ortho*-position and the hydrophobicity of the organic solvent caused a decrease in the reactivity and selectivity.

The best conditions were applied to resolve a stereoisomeric mixture *cis*/*trans*-2-phenyl-1-cyclohexanol and its corresponding acetate in acylation and deacylation. The obtained results showed the highly enantio- and diastereoselectivity of the CAL-B during the acylation and the deacylation in favor of the *trans*-(*R*)-enantiomer product to the detriment of the *cis*-isomer which does not react. The CAL-B catalyzed resolution of mixture *cis*–*trans*-2-arylcyclohexanols is an easy and convenient approach to provides only one stereoisomer of a mixture of four with high enantiomeric excess.

4. Experimental

4.1. General

All reagents purchased from either: Aldrich, Acros, TCI or Alfa Aesar were used as received. The *Candida antarctica lipase* immobilized on acrylic resin CAL-B was purchased from Aldrich. Specific activity >10,000 U/g used without any pre-treatment. Reactions were monitored by thin-layer chromatography (TLC) carried out on Silica gel $60F_{254}$ plates type *MERCK* 5179, 250 *mesh*, using UV light (254 nm) as the visualizing agent. NMR spectra were recorded on Bruker spectrometers (300 MHz for ^1H, 75 MHz for ^{13}C) instrument and calibrated using residual deuterated solvent as an internal reference (peak at 7.26 ppm in ^1H NMR and 3 peaks at 77 ppm in ^{13}C NMR in the case of $CDCl_3$). The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet–doublet. Chemical shifts were expressed in ppm and coupling constant (*J*) in Hz. Melting points were measured using BÜCHI MELTING POINT B-545. The mass spectra were obtained using FINNIGAN-MAT TSQ 7000 and FINNIGAN-MAT LQC spectrometers. The enantiomeric excesses were measured by a chiral stationary phase HPLC: Chiralpak®AD (4.6 × 250 mm) and Chiralpak®IA (4.6 × 250 mm) column; or by gas chromatography (ThermoFinnigan Trace GC) equipped with an automatic autosampler and using a CHIRALSIL-DEX CB column (25 m; 0.25 mm; 0.25 μm). Retention times are reported in minutes. Optical rotations were determined using a Perkin-Elmer 341 Polarimeter at room temperature using a cell of 1 dm length and λ = 589 nm.

4.2. Synthesis procedures of all racemic compounds and their NMR data

The *trans*-2-phenylcyclohexanol **2a** is commercially available, whereas the rest of the alcohols were prepared by opening of cyclohexene oxide in the presence of Grignard reagent and a catalytic amount of copper salts (I).

4.2.1. Synthesis procedure of racemic *trans*-2-arylcyclohexanols 2b–2d

To a stirred refluxing suspension of 0,26 g of Magnesium turning (10.7 mmol, 1 equiv) in 1.5 mL of dry THF, under an argon atmosphere, was added dropwise a solution of 10 mmol (1 equiv) of the appropriate bromoaryl diluted in 15 mL of THF. A drop of dibromoethane was also added to initiate the reaction. After 1 h of stirring, the solution was cooled to −78 °C and a suspension of copper chloride(I) (48 mg, 0.045 equiv) was added. Ten minutes later, a mixture of cyclohexene oxide (0.75 ml, 0.7 equiv) in 3 mL of THF was added dropwise and stirred for ten minutes at the same temperature. The temperature was then gradually raised to ambient temperature with stirring overnight. For the treatment, the reaction mixture was quenched with 15 mL of saturated NH_4Cl and 10 mL of diethyl ether were added. The organic layer was washed with brine and dried over magnesium sulphate, filtered and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography on silica gel (50/50 diethyl ether/petroleum ether).

4.2.1.1. *trans*-2-(2-Methoxyphenyl)-cyclohexanol 2b. Molecular formula: $C_{13}H_{18}O_2$ 206.28 g/mol; white crystals; yield = 60% Melting point: 56.7 °C; R_f = 0.67. (Cyclohexane/Ethyl acetate: 80/20). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.33–1.54 (m_a, 4H,

cycle), 1.97–1.85 (m_a, 4H, cycle), 2.14–2.17 (m_a, 1H, cycle), 2.98–3.07 (m_a, 1H, cycle), 3.72–3.8 (m_a, 1H, cycle), 3.85 (s, 3H, O-CH_3), 6.9–7.01 (m_a, 2H aromatics), 7.2–7.3 (m_a, 2H aromatics); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 157.8, 131.6, 127.5, 127.4, 121.1, 110.9, 74.1, 55.6, 45.1, 35.3, 32.4, 26.3, 25.2; MS (D-ESI; *m*/*z*): 229.68 ([M+Na]$^+$, 100%).

4.2.1.2. *trans*-2-Biphenyl-4-yl-cyclohexanol 2c. Molecular formula: $C_{18}H_{20}O$ 252.15 g/mol; white crystal, yield = 69%; Melting point: 131.2 °C; R_f = 0.69 (Petroleum ether/Ethyl acetate: 80/20). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.38–1.67 (m, 4H, cycle), 1.85 (s, 2H, cycle), 1.93–1.98 (m, 2H, cycle), 2.17–2.21 (m, 1H, OH), 2.50–2.58 (m_a, 1H cycle), 3.70–3.78 (m_a, 1H, cycle), 7.37–7.44 (m, 3H aromatics), 7.48–7.05 (m, 2H aromatics), 7.61–7.68 (m, 4H aromatics); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 144.6, 140.9, 139.7, 128.8, 128.4, 127.4, 127.2, 127, 74.4, 52.8, 34.6, 33.4, 26.1, 25.1; HRMS (D-ESI; *m*/*z*): 275.14 ([M+Na]$^+$, 100%).

4.2.1.3. *trans*-2-(Naphthalen-2-yl)-cyclohexanol 2d. Molecular formula: $C_{16}H_{18}O$ 226.14 g/mol**;** yellow solid, yield = 77%; Melting point: 93.8 °C; R_f = 0.53 (Dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.34–1.54 (m, 3H cycle), 1.58–1.73 (m, 1H cycle), 1.83–187 (m, 2H cycle), 1.92–1.99 (m, 2H cycle), 2.15–2.20 (m, 1H cycle), 2.59–2.68 (m, 1H-OH), 3.73–3.81 (m, 1Hcycle), 7.41–7.45 (dd, *J* = 8.5 & 1.6 Hz, 1Haromatics), 7.48–7.57 (m, 2H aromatics), 7.76–7.88 (m, 4H aromatics). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 140.8, 133.6, 132.6, 128.4, 127.7, 126.6, 126.1, 126, 125.5, 74.2, 53.3, 34.5, 33.4, 26.1, 25.1; HRMS (D-ESI; *m*/*z*): 249.12 ([M+Na]$^+$, 100%).

4.2.2. Synthesis of isomeric mixture *cis*/*trans*-2-phenyl-1-cyclohexanol 2a

The racemic alcohol mixture was obtained after reduction of 1 equiv of the corresponding ketone (1 g, 5.7 mmol diluted in 35 mL of THF), using 6 equiv of $NaBH_4$ (1.3 g, 34.4 mmol) in (THF/H_2O, 4/1 v/v, 52 mL/13 mL). The reaction mixture was stirred under at 0 °C. The evolution of the reactions was monitored by TLC. After the total consumption of the ketone, the reaction mixture was neutralized by HCl (1 M), and the THF was evaporated. Then, the alcohol was extracted from water by ethyl acetate and the organic layers was dried with $MgSO_4$ and evaporated in vacuo. The resulting isomeric mixture of the alcohol was obtained pure as white solid in 75% yield.

4.2.2.1. *cis*/*trans*-2-Phenyl-1-cyclohexanol 2a. Molecular formula: $C_{12}H_{16}O$ 176.12 g/mol. Melting point: 53.3 °C. R_f = 0.5 (Cyclohexane/Ethyl acetate 80/20). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.33–1.87 (m, 11H, cycle + OH), 1.91–2.13 (m, 1H, cycle), 2.46–2.75 (m, 1H, HC-OH), 3.64–4.04 (m, 1H, HC-Ph), 7.02–7.61 (m_a, 5H aromatics); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 143.3, 128.8, 128.6, 128, 127.8, 126.9, 74.5, 53.2, 34.5, 33.4, 26.1, 25.1

4.2.3. Procedure for the synthesis of racemic 2-arylcyclohexyl acetates 3a–3d

The arylcyclohexyl acetates were synthesized by classical chemical acylation via the corresponding *racemic trans*-arylcyclohexanol alcohol (1 equiv), using 2 equiv of anhydride acetic, 2 equiv of Et_3N, and a catalytic amount of 4-dimethylaminopyridine (0.2 equiv) in 1 mL of diethyl ether. The final products were obtained pure after standard work-up in excellent yields. All structure was confirmed by the ^{1}H and ^{13}C NMR spectra.

4.2.3.1. *cis*/*trans*-2-Phenyl-cyclohexyl acetate 3a. Molecular formula: $C_{14}H_{18}O_2$ 218.29 g/mol; crude oil, yield = 77%; R_f = 0.79 (Cyclohexane/Ethyl acetate 80/20). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.2–1.9 (m_a, 10H cycle + 3H—OC—CH_3), 2.1–2.2 (m, 1H, cycle), 2.6–2.75 (m, 1H, HC—OAc), 4.9–5.1 (m, 1H, HC—Ph), 7.1–7.3 (m, 5H aromatics); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm) = 170.4, 143.1, 128.2, 127.5, 126.4, 119.9, 75.9, 49.7, 33.8, 32.3, 25.8, 24.8, 21.

4.2.3.2. *trans*-2-Phenyl-cyclohexyl acetate 3a. Molecular formula: $C_{14}H_{18}O_2$ 218.29 g/mol; crude oil, yield = 77%; R_f = 0.79 (Cyclohexane/Ethyl acetate 80/20). ^{1}H NMR (300 MHz, CDCl3): δ (ppm) = 1.3–1.66 (ma, 4H cycle), 1.99 (s, 3H, O—C—CH_3), 1.82–1.98 (ma, 1H, cycle), 2.11–2.23 (ma, 1H cycle), 2.63–2.93 (m, 1H cycle), 4.95–5.03 (ma, 1H cycle), 7.19–7.31 (ma, 5H aromatic); ^{13}C NMR (75 MHz, CDCl3) δ (ppm) = 170.4, 143.2, 128.3, 127.5, 126.4, 75.9, 49.8, 33.8, 32.4, 25.9, 24.8, 21.

4.2.3.3. *trans*-2-(2-Methoxy-phenyl)-cyclohexyl acetate 3b. Molecular formula: $C_{15}H_{20}O_3$ 248,32 g/mol; white crystals, yield = 78%; Melting point: 71.2 °C; R_f = 0.71, cyclohexane/Ethyl acetate: (80/20); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.28–1.55 (m_a, 5H cycle), 1.77 (s, 3H, O—C—CH_3), 1.83–1.93 (m_a, 2H cycle), 2.10–2.26 (m_a, 1H cycle), 3.15–3.22 (m_a, 1H cycle) 3.82 (s, 3H, O—CH_3), 5.12–5.20 (m_a, 1H cycle), 6.73–6.82 (q, *J* = 8.7 Hz, 2H aromatics), 7.03–7.09 (m_a, 2H aromatics); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 170.4, 157.3, 131.3, 127.1, 127, 120.6, 110.6, 74.8, 55.4, 32.8, 32.4, 25.9, 24.8, 20.9.

4.2.3.4. *trans*-([1,1′-Biphenyl]-4-yl)-cyclohexyl acetate 3c. Molecular Formula: $C_{20}H_{22}O_2$ 294.16 g/mol; yellow crystal, yield = 90%; Melting point: 98.5 °C; R_f = 0.92, (Petroleum ether/Ethyl acetate: 80/20). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.36–1.48 (m, 2H cycle), 1.49–1.62 (m, 2H cycle), 1.84 (s, CO—CH_3, 3H), 1.86 (m, 3H, cycle), 2.17 (m, 1H, cycle), 2.68–2.76 (m, 1H cycle), 4.98–5.05 (m, 1H, cycle), 7.26–7.61 (m, 9H aromatics); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 142.4, 141, 139.2, 128.8, 128, 127.1, 127, 75.9, 49.4, 34, 32.4, 25.9, 24.8, 21.1. HRMS (D-ESI; *m*/*z*): 317.151 ([M+Na]$^+$, 100%).

4.2.3.5. *trans*-2-(Naphthalen-2-yl)-cyclohexyl acetate 3d. Molecular formula: $C_{18}H_{20}O_2$ 268.15 g/mol; yellow solid, yield = 92%; R_f = 0.86 (Dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.99–1.08 (m_a, 2H cycle), 1.11–1.27 (m_a, 2H cycle); 1.29 (s, 3H, O—CH_3), 1.36–1.48 (m_a, 2H cycle), 1.54–1.60 (m_a, 1H cycle), 1.77–1.82 (m_a, 1H cycle), 2.7–2.79 (m, 1H cycle), 4.71–4.79 (m, 1H cycle), 6.96–7.06 (m_a, 3H, aromatic), 7.35–7.40 (m_a, 4H aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170, 140.5, 132.3, 132.2, 127.7, 127.5, 127.4, 125.8, 125.7, 125.1, 75.5, 49.6, 33.8, 32.2, 25.7, 24.6, 20.7; HRMS (D-ESI; *m*/*z*): 291.13 ([M+Na]$^+$, 100%).

4.3. Enzymatic kinetic resolutions procedures

4.3.1. Enzymatic acylation

All enzymatic acylation reactions were performed using 1 equiv of racemic alcohol and 3 equiv of the appropriate acetyl donor dissolved in 2 mL of solvent. Next, 200 mg of CAL-B were added and the mixture was shaken at room temperature for 24 h. After removal of the enzyme by filtration and evaporation of the solvent, the reaction mixture was purified by flash chromatography (petroleum ether/EtOAc: 8/2) to separate the obtained arylcyclohexylacetate and the furnished *trans*-aryl cyclohexyl acetate. The two optically active compounds were analyzed by chiral HPLC or CG.

4.3.2. Enzymatic hydrolysis using carbonate salts

In a typical procedure, 1 mmol of racemic aryl cyclohexyacetate was dissolved in 2 mL of solvent before the addition of 1 mmol of sodium carbonate and 200 mg of CAL-B. The mixture was shaken at 40 °C for 72 h. After removal of the enzyme by filtration and evaporation of the solvent, the reaction mixture was purified by flash

chromatography (Petroleum ether/EtOAc: 8/2) to separate the residual arylcyclohexylacetate and the furnished *trans*-arylcyclohexanol alcohol. The two optically active compounds were analyzed by chiral HPLC or CG.

4.4. Chiral GC analysis and/or chiral HPLC analysis

The absolute configurations of all chiral compounds (isolated after chromatography) were determined by polarimetry by comparison with literature's data. The conditions for the analysis of alcohols and acetates are reported below:

4.4.1. (1*S*,2*R*)-(+)-2-Phenyl-1-cyclohexanol 2a

GC (Chiralsil-Dex CB,): t_1 = 9.04 min, t_2 = 9.61 min (T_{column} = 155 °C, flow 1.2 mL/min). $[\alpha]_D^{20}$ = +45 (*c* 0.1, CH_2Cl_2) for 89% ee, [Lit. $[\alpha]_D$ = −58.6 (*c* 1.19, MeOH) for 99% ee (1*R*,2*S*)].[14]

4.4.2. (1*R*,2*S*)-(−)-2-Phenylcyclohexyl acetate 3a

GC (Chiralsil-Dex CB,): t_1 = 8.56 min, t_2 = 8.77 min (T_{column}=155 °C, flow 1.2 mL/min). $[\alpha]_D^{20}$ = −7 (*c* 0.1, CH_2Cl_2) for 99% ee, [Lit. $[\alpha]_D$ = −6.5 (*c* 0.32, EtOH) for 99% ee (1*R*,2*S*)].[13]

4.4.3. (1*S*,2*R*)-(+)-2-(2-Methoxyphenyl)-cyclohexanol 2b

Chiral HPLC: *Chiralpak* AD column, t_R = 10.33 min; t_S = 14.37 min. Eluant (v,v): hexane/EtOH: 97/3; flow 1 mL/min. $[\alpha]_D^{20}$ = +20 (*c* 0.1, $CHCl_3$) for 42% ee, [Lit. $[\alpha]_D$ = −5 (*c* 1.52, MeOH) for 15% ee (1*R*,2*S*)].[26]

4.4.4. (1*R*,2*S*)-(−)-2-(2-Methoxyphenyl)-cyclohexyl acetate 3b

GC (Chiralsil-Dex CB,): t_1 = 7.86 min, t_2 = 7.99 min (T_{column} = 170 °C, flow 1.2 mL/min). $[\alpha]_D^{20}$ = −2.4 (*c* 0.1, $CHCl_3$) for 99% ee.

4.4.5. (1*R*,2*S*)-(−)-2-([1,1′-Biphenyl]-4-yl)-cyclohexanol 2c

Chiral HPLC: *Chiralpak* IA column, t_{RD}10.11 min; t_{SD}18.43 min. Eluant (v,v): iso-hexane/EtOH: 90/10; flow 1 mL/min. $[\alpha]_D^{20}$ = −41 (*c* 0.03, CH_2Cl_2) for 99% ee.

4.4.6. (1*R*,2*S*)-(−)-2-([1,1′-Biphenyl]-4-yl)-cyclohexyl acetate 3c

Chiral HPLC: *Chiralpak* IA column, t_R = 4.44 min; t_S = 5.06 min. Eluant (v,v): iso-hexane/EtOH: 90/10; flow 1 mL/min. $[\alpha]_D^{20}$ = −5 (*c* 0.05, CH_2Cl_2) for 99% ee.

4.4.7. (1*R*,2*S*)-(−)-2-(Naphthalen-2-yl)-cyclohexanol 2d

Chiral HPLC: *Chiralpak* IA column, t_R = 10.11 min; t_S = 18.43 min. Eluant (v,v): iso-hexane/EtOH: 90/10; flow 1 mL/min. $[\alpha]_D^{20}$ = −24 (*c* 0.05, CH_2Cl_2) for 99% ee, [Lit. $[\alpha]_D$ = −7.8 (*c* 1.05, $CHCl_3$); 33% ee (1*R*,2*S*)].[27]

4.4.8. (1*R*,2*S*)-(+)-2-(Naphthalen-2-yl)-cyclohexyl acetate 3d

Chiral HPLC: *Chiralpak* IA column, t_R = 7.59 min; t_S = 7.99 min. Eluant (v,v): iso-hexane/-PrOH: 98/2; flow 0.7 mL/min. $[\alpha]_D^{20}$ = +32.8 (*c* 0.1, CH_2Cl_2) for 99% ee, [Lit. $[\alpha]_D$ = +32.6 (*c* 1.05, $CHCl_3$); 99% ee (1*R*,2*S*)].[10]

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A. Supplementary data

Supplementary data (all experimental details, characterization spectra (NMR and chiral chromatography) of all synthesized product) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.09.010.

References

1. (a)*Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; Blaser, H. U., Federsel, H. J., Eds., 2nd ed; John Wiley & Sons: Weinheim, 2011; (b) Gotor-Fernández, V.; Brieva, R.; Gotor, V. *J. Mol. Catal. B Enzym.* **2006**, *40*, 111–120; (c) Ghanem, A.; Aboul-Enein, H. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3331–3351.
2. Whitesell, J. K.; Chen, H. H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663–4664.
3. (a) Vasconcellos, M. L.; Desmaële, D.; Costa, P. R.; D'Angelo, J. *Tetrahedron Lett.* **1992**, *33*, 4921–4922; (b) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953–964; (c) Potin, D. J. *J. Am. Chem. Soc.* **1990**, *112*, 3483–3486; (d) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985–7012.
4. Brown, H. C.; Vara Prasad, J. V. N.; Gupta, A. K.; Bakshi, R. *J. Org. Chem.* **1987**, *52*, 310–311.
5. Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378–4380.
6. (a) Zhao, S. H. U.S. Patent No. 5,420,366. 1995. Washington, DC: U.S. Patent and Trademark Office.; (b) King, S. Bruce; Barry Sharpless, K. *Tetrahedron Lett.* **1994**, *35*, 5611–5612.
7. Asensio, G.; Cuenca, A.; Rodriguez, N. *Tetrahedron: Asymmetry* **2003**, *14*, 3851–3855.
8. Matsugi, M.; Hagimoto, Y.; Nojima, M.; Kita, Y. *Synth. Commun.* **2013**, *43*, 1425–1431.
9. Wang, Li.; Akhani, Ravish K.; Wiskur, Sheryl L. *Org. Lett.* **2015**, *17*, 2408–2411.
10. Takahashi, Michiyasu.; Ogasawara, Kunio. *Tetrahedron: Asymmetry* **1995**, *6*, 1617–1620.
11. Carpenter, Bryon E. *Tetrahedron: Asymmetry* **1996**, *7*, 3107–3108.
12. Celia, E. C.; Cernia, E.; D'Acquarica, I.; Palocci, C.; Soro, S. *J. Mol. Catal. B Enzym.* **1999**, *6*, 495–503.
13. She, Y. H.; Wu, C. F.; Shia, K. S.; Wu, J. D.; Peddinti, R. K.; Liu, H. J. *Synthesis* **2005**, *5*, 749–752.
14. Basavaiah, D.; Rao, P. *Tetrahedron: Asymmetry* **1994**, *5*, 223–234.
15. (a) Busto, E.; Gotor-Fernandez, V.; Gotor, V. *Chem. Soc. Rev.* **2010**, *39*, 4504–4523; (b) Faber, K. *Biotransformations in Organic Chemistry*, 6th ed.; Springer: Berlin Heidelberg, 2011.
16. (a) Bouzemi, N.; Grib, I.; Houiene, Z.; Aribi-Zouioueche, L. *Catalysts* **2014**, *4*, 215–225; (b) Zaïdi, A.; Merabet-Khelassi, M.; Aribi-Zouioueche, L. *Catal. Lett.* **2015**, *145*, 1054–1061.
17. Merabet-Khellassi, M.; Aribi-Zouioueche, L. *Tetrahedron: Asymmetry* **2009**, *20*, 1371–1377.
18. Merabet-Khelassi, M.; Houiene, Z.; Aribi-Zouioueche, L. *Tetrahedron: Asymmetry* **2012**, *23*, 828–833.
19. Houiene, Z.; Merabet-Khelassi, M.; Bouzemi, N.; Riant, O. *Tetrahedron: Asymmetry* **2013**, *24*, 290–296.
20. Alalla, A.; Merabet-Khelassi, M.; Riant, O. *Tetrahedron: Asymmetry* **2016**, *27*, 1253–1259.
21. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
22. (a) Chen, C. S.; Fujimoto, Y.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299; (b) Kagan, H. B.; Fiaud, J.-C. Kinetic Resolution. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; ; J. Wiley & Sons: New York, 1988; Vol. 18, pp 249–330.
23. Aribi-Zouioueche, L.; Fiaud, J. C. *Tetrahedron Lett.* **2000**, *41*, 4085–4088.
24. (a) Levy, L. M.; Dehli, J. R. *Tetrahedron: Asymmetry* **2003**, *14*, 2053–2058; (b) Levy, L. M.; Lavandera, I.; Gotor, V. *Org. Biomol. Chem.* **2004**, *2*, 2572–2577.
25. Tanikaga, R.; Matsumoto, Y.; Sakaguchi, M.; Koyama, Y.; Ono, K. *Tetrahedron Lett.* **2003**, *44*, 6781–6783.
26. Vrancken, E.; Alexakis, A.; Mangeney, P. *Synlett* **2005**, 1354–1366.
27. Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699–10708.