Article

Enantiocomplementary Preparation of (*S*)- and (*R*)-Arylalkylcarbinols by Lipase-Catalysed Resolution and Mitsunobu Inversion: Impact of Lipase Amount

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Abstract: A series of arylalkylcarbinol derivatives were deracemized through sequential combination of *Candida antarctica* lipase B (CAL-B) catalyzed resolution by hydrolysis and Mitsunobu stereoinversion. The (*S*)-acetates were obtained in 71%–99% *ee* and 76%–89% yields. An enantiocomplementarity was established for the hydrolysis and acylation reactions with CAL-B lipase. Thus, the (*S*) and (*R*) enantiomers of Indan-1-yl acetate, 1,2,3,4-tetrahydro-1-naphthalenol acetate and 1-(2-naphthyl) ethyl acetate were obtained in 91%–99% *ee* and 76%–89% yield.

Keywords: deracemisation; lipase; hydrolysis; stereoinversion; arylalkylcarbinol

1. Introduction

The development of efficient methods for the synthesis of enantiomerically pure alcohols is of tremendous importance [1–3]. They are important intermediates for the synthesis of pharmaceuticals, agrochemicals, pheromones, flavors, liquid crystals and chiral auxiliaries in asymmetric synthesis [4,5]. As an option for sustainability, chemists have continued to be attracted to the area of biocatalysts that have been increasingly used to attain enantiomerically enriched or pure secondary alcohols [6,7]. High stability, enantioselectivity and good commercial availability in free and immobilized forms have made

lipases (EC 3.1.1.3) especially attractive kinetic resolution catalysts via the acylation [8,9]. Unlike other enzymes, lipases can also exhibit catalytic activity in biphasic media [10].

However, even in the case where the enantioselectivity factor is high ($E > 100$), the most striking limitation, common to strategies relying on kinetic resolution, is the maximum theoretical yield of 50% for a single enantiomer. In order to circumvent this constraint associated with the yield, several approaches have been developed, which render an enantio-convergent process delivering a single enantiomeric product in 100% theoretical yield [11–13]. Methods based on a dynamic kinetic resolution imply *in situ* transition-metal-catalyzed racemization of the slowly reacting enantiomer combined with kinetic resolution process [14–16]. Another strategy has been performed that allows selective inversion of configuration of one enantiomer via a microbial process [17,18] or a chemo-enzymatic protocol [19,20]. In the latter case, special emphasis is devoted to the deracemization of sec-alcohols and their derivatives [21]. In this field, one of the most versatile stereo chemical transformations is the Mitsunobu reaction [22]. It was found that the inversion of the configuration of chiral secondary alcohols following an enzymatic kinetic resolution step was of fruitful application [23,24].

In our previous study [25], we applied a lipase-catalyzed acylation, in presence of an immobilized lipase from *Candida antarctica* B, followed by Mitsunobu chemical stereoinversion to a series of arylalkylcarbinols. The corresponding (*R*)-acetates were obtained in good yields and enantiomeric excesses. These results urged us to explore the possibility of extending such a process to kinetic resolution by hydrolysis in order to obtain the (*S*)-acetates (Scheme 1). Our study has been realized mainly for the sake of comparison and also to emphasize the enantiocomplementarity of the two biocatalyzed reactions, acylation and hydrolysis, in presence of the same lipase. This comparison offers an additional catalysis tool; the strategy (acylation/inversion or hydrolysis/inversion) can be adapted to the desired enantiomer.

Scheme 1. Lipase hydrolysis combined to Mitsunobu stereoinversion.
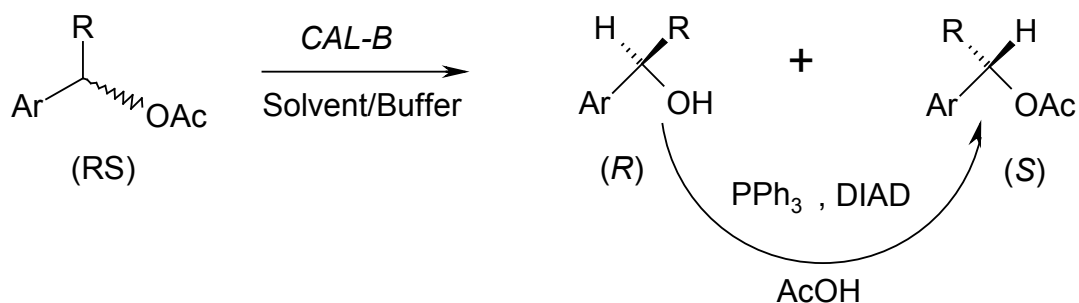
Few lipases showed excellent enantiocomplementary hydrolysis and acylation due to lower enantioselectivities disclosed generally after hydrolysis reaction in presence of the same enzyme [26,27]. Accordingly, enantiocomplementaritry between the two reactions is finding scant attention in the literature [28,29]. This efficient pathway has been reported previously in presence of *Pseudomonas fluorescens* lipase (PFL) [30].

Enzymatic hydrolysis in a biphasic medium is generally described with moderate selectivity in the literature. The amount of lipase is an important parameter for improving the enzymatic selectivity when studying the kinetic acylation [25,31]. The influence of this parameter was not examined previously in hydrolysis in biphasic media.

2. Results and Discussion

2.1. Optimization of the Lipase Amount

Before starting the deracemization process, we thought useful to study the effect of the amount of enzyme on activity and selectivity of hydrolysis reaction. In a recent report, our data confirmed the importance of decreasing the enzyme amount in order to enhance the enantioselectivity in the kinetic transesterification of a series of arylalkylcarbinols [31].

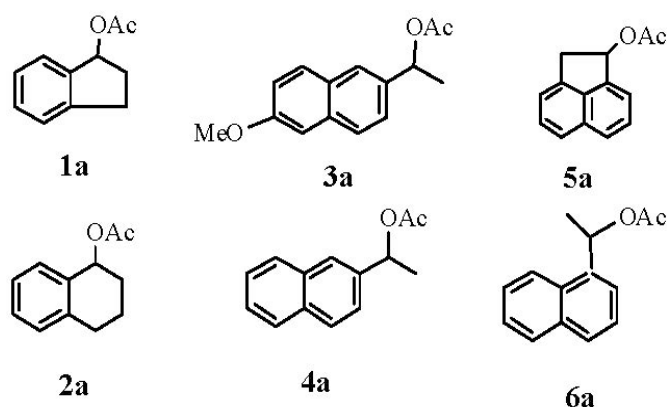**Scheme 2.** Substrate models.

Table 1. Enzymatic hydrolysis of acetates **1a–6a**. The shadowed lines emphasize the best results with high reactivities and selectivities (*C* and *E*).

Entry	Substrate [a]	*CAL-B* (mg)	ee_S (%) [b]-(*S*) [d]	ee_P (%) [b]-(*R*) [d]	*C* % [c]	*E* [c]
1		150	44	96	32	76
2	**1a**	12	98	99	50	>500
3		6	79	93	46	67
4		150	83	98	46	>200
5	**2a**	50	99	99	50	>500
6		20	28	96	23	64
7	**3a**	150	98	99	50	>500
8		20	99	98	50	>500
9	**4a**	150	89	99	47	>500
10		20	99	97	50	>500
11		150	7	99	6	>200
12	**5a**	60	10	96	9	54
13		20	-	-	-	-
14		150	75	87	46	32
15	**6a**	60	51	99	34	70
16		20	44	99	30	>200

[a] Reactions were carried out with 1mmol of racemic acetate in diethyl ether/buffer solution pH = 7: (1/4) at 25 °C, in the presence of a catalytic amount of *CAL-B* (4500 U/g), for 48 h (72 h entries 12–16); [b] Measured by HPLC using Chiracel OD-H column; [c] Conversion $C = ee_s /ee_s + ee_p$; selectivity factor $E = \ln [(1 - C) (1 - ee_s)]/\ln[(1 - C) (1 + ee_s)]$; [d] Absolute configuration was determined by comparison of the sign of the specific rotation of the isolated product with the literature (see experimental).

The enzymatic hydrolysis of racemic secondary aromatic acetates **1a**–**6a** (Scheme 2), which are also our study models, is carried out in biphasic system: phosphate buffer/diethyl ether (*v/v*) (1:4) pH = 7, in the presence of variable amounts of *Candida antarctica* lipase fraction B immobilized on acrylic resin (*CAL-B*) used previously [25]. After the appropriate time; a mixture of unreacted (*S*) acetate and formed (*R*) alcohol was obtained. The results are shown in Table 1.

The results from (Table 1) indicate the important influence of *CAL-B* on both reactivity and selectivity depending directly on the enzyme loading in the cases of substrates **1a** and **2a** (entries 1–6). Thus, decreasing the amount of the lipase from 150 mg to 12 mg for **1a** and to 50 mg for **2a** improves both reactivity and selectivity and the (*R*)-alcohols are obtained with excellent enantiomeric excesses (entries 2 and 5). Reducing the amount of *CAL-B* to lower values (entries 3 and 6) displays a negative effect on both reactivity and selectivity which drop dramatically, especially in the case of substrate **2a** (entry 6).

On the other hand, we did not observe any change in activity or selectivity of the lipase by decreasing its amount to eight times its initial value with acetates **3a** and **4a** (entries 8 and 10), excellent enantioselectivities were reached in all cases (*E* > 500). For substrate **5a**, the hydrolysis reaction did not afford good results. Despite the observed high enantioselectivity by using 150 mg of enzyme (entry 11), the conversion was very low and no reaction was detected when using 20 mg of lipase. The hydrolysis of acetate **6a** proceeded with a good selectivity *E* > 200 by using 20 mg of *CAL-B* (entry 16) and the selectivity diminished by increasing the lipase amount (entries 14 and 15). The *CAL-B* displays (*R*)-enantiopreference since the (*R*)-acetates were selectively hydrolysed in all cases. On the basis of these results, we have shown a noticeable impact of the *CAL-B* amount on the activity and selectivity in the hydrolysis reaction. Thus, a threshold has been established for each substrate in order to use the minimum and effective amount of *CAL-B*. This study shows the important influence of the amount of lipase on the kinetic resolution by hydrolysis.

Few reports dealt with the impact of the enzyme loading and an elucidation of the mechanism is not an easy task since many parameters could be taken into account, such as the enzyme aggregates that might interfere and hinder the selectivity especially in the case of a large quantity [32], or the problems of mass transport limitation that probably hinder diffusion of the enzyme in the reaction medium [33].

2.2. Deracemization by Combined Enzymatic Hydrolysis/Mitsunobu Stereoinversion

It is well recognized that a deracemization process needs to fulfill, in a first step of kinetic resolution, the requirement of reaching a satisfactory enantioselectivity at *C* = 50% substrate conversion. For this reason, we limited our further study of the Mitsunobu inversion combined with hydrolysis in optimal conditions, to substrates **1a**–**4a**. At the appropriate conversion and after removal of the enzyme by filtration, the crude mixture of unreacted (*S*)-acetate and the formed (*R*)-alcohol underwent Mitsunobu reaction. Triphenylphosphine and acetic acid were added to the mixture followed by the addition of diisopropylazodicarboxylate (DIAD) at 0 °C to convert the formed (*R*)-**1**–**4** alcohols into the corresponding (*S*)-**1a**–**4a** acetates. The results are collected in Table 2.

Table 2. Deracemization of acetates **1a**–**4a** through a resolution/inversion process. The shadowed line emphasize the best result in terms of enantiomeric excess and yield.

Substrate [a]	*CAL-B* catalyzed hydrolysis [b]				Mitsunobu inversion	
	CAL-B (mg/mmole)	(*R*)-Alcohol (%*ee*) [c]	(*S*)-Acetate (%*ee*) [c]	E [d]	(*S*)-Acetate (%*ee*)	Yield [e] (%)
1a	25	**99**	**98**	**>500**	94	78
2a	100	**99**	**99**	**>500**	99	89
3a	40	**98**	**99**	**>500**	71	82
4a	40	**97**	**99**	**>500**	92	76

[a] 2 mmol substrate subjected to hydrolysis, in presence of the optimized amounts of lipase, then Mitsunobu reagents; [b] Conversion $C = 49\%$–50% (see Table 1); [c] *ee* determined by HPLC using Chiracel OD-H; [d] Calculated from $ee_{alcohol}$ and $ee_{acetate}$ and conversion *C*; [e] Isolated yield.

All hydrolysis reactions proceeded with an excellent enantioselectivity ($E > 500$). At 50% conversion, both the produced alcohol and the unreacted acetate showed an excellent enantiomeric excess (>99% from **2a**) or good (97%–99% from **1a**, **3a**, **4a**). This was achieved in presence of the adequate amount of *CAL-B* lipase. After the Mitsunobu reaction, no residual alcohol was detected. Except for substrate **3a**, the other acetates showed either an excellent (>99% from **2a**) or good with a slight drop in the enantiomeric excess (92%–94% from **4a** and **1a** respectively). A racemization-induced process under Mitsunobu reagents might give an explanation to the loss of stereoselectivity [34,35]. Both the inversion efficiency and yield depended on the aromatic substituents [36]. Recently, we observed almost full racemization during the nucleophilic substitution reaction due to the presence of an electron donating substituent ring [37].

A comparison between the deracemization process via acylation [25] and the current process combining hydrolysis and Mitsunobu inversion furnished important data (Table 3). Although the significant difference between the optical purities of acetates (*S*)-**3a** (*ee* = 71%) and (*R*)-**3a** (*ee* > 99%), our study pointed out that it is feasible to afford both the enantiomers of acetates **1a**, **2a** and **4a** with good enantiomeric excesses (ee_R = 91%–99%, ee_S = 92%–99%) and satisfying yields (74%–89%).

Table 3. Comparison of deracemization through acylation/inversion and hydrolysis/inversion processes.

Substrate [a]	*CAL-B* Catalyzed Acylation/Mitsunobu Stereoinversion		Substrate [b]	*CAL-B* Catalyzed Hydrolysis/Mitsunobu Stereoinversion		
	CAL-B (mg)	(*R*)-Acetate (%*ee*)	Yield (%)		*CAL-B* (mg)	(*S*)-Acetate (%*ee*)	Yield (%)
1	12	**>99**	**82**	1a	25	**94**	**78**
2	100	**>99**	**79**	2a	100	**99**	**89**
3	40	**>99**	**74**	3a	40	71	82
4	50	**91**	**76**	4a	40	**92**	**76**

[a] 2 mmol substrate, 4 mmol isopropenyl acetate, 10 mL diethyl ether, 24 h, room temperature; [b] 2 mmol substrate, diethyl ether/buffer solution pH = 7: (1/4), 48 h, 25 °C.

It is worth mentioning that an interesting enantiocomplementarity has been established between *CAL-B*-catalyzed acylation and the reaction of hydrolysis. Thus, the two enantiomers of 1,2,3,4-tetrahydronaphthalen-1-yl acetate **2a** and Indan-1-yl acetate **1a** were provided optically pure (*ee* > 99% for **2a**) and (*ee* = 94%–99% for **1a**) with high yields (Scheme 3). These results show the importance of the enantiocomplementarity concept.

Scheme 3. Enantiocomplementary preparation of both enantiomers of acetates **1a** and **2a**.
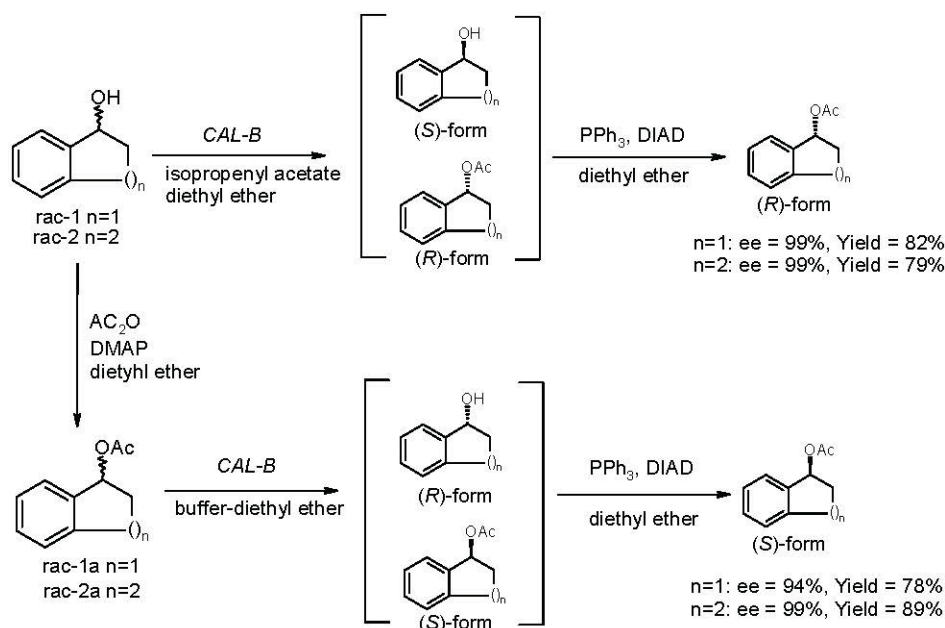
3. Experimental Section

3.1. General

Optical rotations were determined using a Perkin–Elmer (Waltham, MA, USA) 241 Polarimeter at room temperature using a cell of 1 dm length and $k = 589$ nm. The enantiomeric excesses were measured by a chiral stationary phase HPLC on Chiralcel® OD-H column (Chiral Technologies. Europe, Illkirch-Graffenstaden, France). Retention times are reported in minutes.

3.2. General Procedure for the Synthesis of Racemic Acetates **1a**–**6a**

The acetates were synthesized by classical chemical acetylations via the corresponding racemic alcohol (1 equivalent), using 1.5 equivalent of anhydride acetic, 1.2 equivalent of Et_3N, and a catalytic amount of 4-dimethylaminopyridine (0.1 equivalent) in 4 mL of ether. The acetates were obtained pure after standard work-up. The ^1H NMR spectra of these products were in good agreement with the literature.

3.3. General Procedure for the Hydrolysis of Racemic Acetates **1a**–**6a** with CAL-B

Racemic acetates 1a-6a (1 mmol), dissolved in 1.5 mL of diethyl ether, were added to phosphate buffer (6 mL) pH 7 and followed by a variable amount of immobilized lipase from *Candida antarctica* B. The reaction mixture was mechanically stirred at 25 °C for the indicated time (see Table 1). The hydrolysis was stopped by filtering off the enzyme. Diethyl ether was removed under vacuum and the resulting aqueous solution was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure.

3.4. Typical Procedure for Synthesis of Enantiomerically Pure Acetates (S)-**1a**–**4a**

All attempts failed to reach the adequate conversion for acetates **5a** and **6a**. The deracemization process mentioned above was applied only to acetates **1a**–**4a**. Racemic acetates **1a**–**4a** (2 mmol), dissolved in 3 mL of diethylic ether, were added to phosphate buffer (12 mL) pH7 followed by the adjusted amount of immobilized lipase from *Candida antarctica* B. The reaction mixture was then stirred at 25 °C for the indicated time until the conversion reached $C = 50\%$ (see Table 2). The reaction was stopped by filtering off the solid enzyme on Celite and the solvent evaporated under reduced pressure. The aqueous solution was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude mixture of the (*S*)-acetate and unreacted (*R*)-alcohol was dissolved in 4 mL of diethyl ether. To this solution were added AcOH (0.144 g, 2.4 mmol) and PPh_3 (0.628 g, 2.4 mmol). The reaction mixture was immediately cooled to 0 °C and a solution of diisopropyl azodicarboxylate (DIAD) (0.48 g, 2.4 mmol) was added dropwise, under vigorous stirring during 20 min. The mixture was allowed to warm to room temperature and stirred for 24 h. Concentration of reaction mixture *in vacuo* followed by silica gel column chromatographic purification of the residue using hexane and ethyl acetate (8:2) gave only the acetates (*S*)-**1a**–**4a** in 76%–89% yields.

3.5. The Conditions for the Analysis of Alcohols (R)-**1**–**6** Are Reported Below

1: (*R*)-(−)-Indan-1-ol: HPLC (Chiralcel® OD-H), $t_R = 37.02$ min; $t_S = 43.24$ min; (Hexane/i-PrOH 98:2 flow: 0.5 mL/min). $[\alpha]_D = -16.7$ (c 1, MeOH).

2: (*R*)-(−)-1,2,3,4-Tetrahydro-1-naphthalenol: HPLC (Chiralcel® OD-H), $t_R = 15.82$ min; $t_S = 17.64$ min; (hexane/i-PrOH 95:5, flow: 0.5 mL/min). $[\alpha]_D = -28.1$(c 2, MeOH).

3: (*R*)-(+)-1-(6-Methoxy-2-naphthyl) ethanol: HPLC (Chiralcel® OD-H), $t_R = 19.47$ min; $t_S = 26.69$ min; (hexane/i-PrOH 90:10, flow: 0.5 mL/min). $[\alpha]_D = +36.4$ (c 0.8, EtOH).

4: (*R*)-(+)-1-(2-Naphthyl) ethanol: HPLC (Chiralcel® OD-H), $t_R = 30.54$ min; $t_S = 33.71$ min; (hexane/i-PrOH 95:5, flow: 0.5 mL/min). $[\alpha]_D = +36.5$ (c 1, MeOH).

5: (*R*)-(−)-1-Acenaphthenol: HPLC (Chiralcel® OD-H), $t_R = 28.80$ min; $t_S = 34.67$ min; (hexane/i-PrOH 95:5, flow: 0.5 mL/min). $[\alpha]_D = -1.4$ (c 2.6, CHCL$_3$).

6: (*R*)-(+)-1-(1-Naphthyl) ethanol: HPLC (Chiralcel® OD-H), $t_R = 20.05$ min; $t_S = 28.90$; (hexane/i-PrOH 90:10, flow: 0.5 mL/min). $[\alpha]_D = +66.5$ (c 1, MeOH).

3.6. The Conditions for the Analysis of Acetates (S)-**1a**–**6a** Are Reported Below

1a: (*S*)-(+)- Indan-1-yl acetate: HPLC (Chiralcel® OD-H), $t_S = 10.14$ min; $t_R = 11.18$ min; (Hexane/i-PrOH 98:2 flow: 0.5 mL/min). $[\alpha]_D = -110.1$ (c 2, CHCl$_3$).

2a: (*S*)-(+)-1,2,3,4-Tetrahydro-1-naphthalenol acetate: HPLC (Chiralcel® OD-H), $t_S = 8.62$ min; $t_R = 9.05$ min; (hexane/i-PrOH 95:5, flow: 0.5 mL/min). $[\alpha]_D = -112.8$ (c 2, CHCl$_3$).

3a: (*S*)-(−)-1-[2-(6-Methoxynaphthyl)] ethyl acetate: HPLC (Chiralcel® OD-H), $t_S = 10.78$ min; $t_R = 12.05$ min; (hexane/i-PrOH 90:10, flow: 0.5 mL/min). $[\alpha]_D = -110$ (c 1, EtOH).

4a: (*S*)-(−)-1-(2-Naphthyl) ethyl acetate: HPLC (Chiralcel® OD-H), $t_S = 10.47$ min; $t_R = 11.98$ min; (hexane/i-PrOH 95:5, flow: 0.5 mL/min). $[\alpha]_D = -110.2$ (c 1, CHCl$_3$).

5a: (*S*)-(+)-1-Acenaphthylenol-1,2-dihydro acetate: HPLC (Chiralcel® OD-H), t_S = 11.88 min; t_R = 12.52 min; (hexane/i-PrOH 95:5, flow: 0.5 mL/min). $[\alpha]_D$ = −85.9 (c 2.4, CHCL$_3$).

6a: (*S*)-(−)-1-(1-Naphthyl)ethyl acetate: HPLC (Chiralcel® OD-H), t_S = 9.87 min; t_R = 13.50 min; (hexane/i-PrOH 90:10, flow: 0.5 mL/min). $[\alpha]_D$ = −49.5 (c 1, CHCl$_3$).

4. Conclusions

In this study, we have displayed the importance of the enantiocomplementarity concept and the efficient routes of access to the *R* and *S* enantiomers of the models studied by comparing the chemoenzymatic deracemization via a sequence of hydrolysis/acylation with CAL-B, combined with esterification using Mitsunobu protocol.

We have performed the kinetic resolution of a series of racemic-arylalkylcarbinol acetates **1a–6a** via hydrolysis catalysed by *CAL-B* lipase. The optimization of *CAL-B* amount is of great importance. We studied this parameter aiming precisely to increase selectivity of our models. For each substrate, the optimum amount of *Candida antarctica* lipase fraction B (CAL-B) was determined to increase the selectivity in hydrolysis reaction in biphasic media conditions.

The convenient amount of lipase has been used in a deracemization process combining kinetic resolution by hydrolysis and a chemical *in situ* stereoinversion for substrates **1a–4a**. The target (*S*)-arylalkylcarbinol acetates were obtained in excellent enantiomeric purity *ee* > 99% for **2a** to good, *ee* = 94% for **1a**, *ee* = 92% for **4a** and *ee* = 71% for **3a** and in good yields (76%–89%). Thus, the Racemic acetates **1a–4a** have been resolved in an enantiocomplementary way by kinetic acylation and hydrolysis reactions using the *Candida antarctica* Lipase B. This enantiocomplementarity offers an additional catalysis tool; the strategy (acylation/inversion or hydrolysis/inversion) can be adapted to the desired enantiomer providing it in a quantitative yield.

Author Contributions

The ideas in this manuscript arose as the result of many conversations among the Nassima Bouzemi and Louisa Aribi-Zouioueche. Nassima Bouzemi wrote the first draft of the manuscript that was then extensively improved by Louisa Aribi-Zouioueche and as the result of comments from our reviewers. Experimental work was carried out by Ismahane Grib and Zahia Houiene. Each member participated sufficiently in the work to take responsibility of the content.

Conflicts of Interest

The authors declare no conflict of interest.

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