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# Easy kinetic resolution of some β-amino alcohols by *Candida antarctica* lipase B catalyzed hydrolysis in organic media

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ABSTRACT

Herein, we present an easy and eco-friendly pathway to obtain some enantiomerically enriched β-amino alcohols using essentially as β-blockers. The enzymatic hydrolysis is conducted in hydrophobic organic media, assisted by sodium carbonate and CAL-B. We describe a new and effective procedure in terms of the chemo- and enantioselectivity, which allows for the formation of both enantiomers: the 2-acetamido-1-arylacetates and 2-acetamido-1-arylethanols were obtained with high ee values (up to >99%), while the selectivities reached *E* >200. The obtained results show a high CAL-B affinity toward the deacylation of the 2-acetamido-1-arylacetates compared to the acylation one. The structure of the 2-acetamido-1-arylacetates had a significant influence on both reactivity and selectivity of the CAL-B catalyzed deacylation. A multigram scale O-deacylation of racemic 2-acetamido-1-phenylacetate has been carried out, giving access both enantiomers with high enantiomeric purity and good isolated chemical yields.



## 1. Introduction

Enantiomerically pure amino alcohols are an important class of compounds widely used in medicinal chemistry[1] and asymmetric synthesis;[2] they are key building blocks for the synthesis of biologically and pharmacologically active compounds. It is widely reported that the 2-amino-1-aryl alcohol is a common structural motif in biologically active compounds: adrenaline, β-adrenergic blockers, anti-asthma drugs, amphenicol antibiotics, and several bioactive natural products. The structure–activity relationship for ligands interacting with adrenergic receptors showed that the essential structural features for direct activity on the receptors were the 2-amino-1-phenylethanol skeleton, the substituent on the phenyl ring and the substituent on the amino group (Fig. 1).[3]

Thus, the design of new eco-compatible access protocols for enantiomerically pure vicinal amino alcohols continues to grow,[4–6] while obeying some greener criteria such as the ease of use, atom economy and energy. One of the most effective target protocols is biocatalysis, which is a sustainable and clean way to get them properly by protection/deprotection of bi- and/or polyfunctional molecules and thus with high chemo-, regio- and stereoselectivity at high TON (turnover number).[7] The strict constraints in pharmaceutical and synthetic applications, require that the chiral amino alcohols have high enantiomeric purity, which in turn requires highly selective asymmetric syntheses or more easily supported by biocatalytic modes.

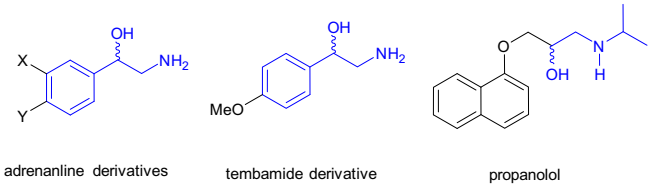


**Figure 1.** Some β-amino alcohols within biological activity.

One of these modes is the enzymatic kinetic resolution of racemic compounds, a widely used technique that presents a green way for the preparation of single-isomer chiral drugs.[8] Hydrolytic enzymes are more frequently used in different industries,[9] especially lipases for the hydrolysis or transesterification reactions.[10] Lipases in particular have proven to be excellent biocatalysts for the resolution of alcohols and amines.[11] Lipases (triacylglycerol acyl hydrolases, EC.3.1.1.3) are one of the most efficient biotools to hydrolyze selectively acylated amino alcohols.[12]

An analysis of the literature data showed that the lipase-catalyzed acylation reactions are the most recently studied;[13] generally it is reported that lipases catalyze, chemoselectively, the N- or O-acylation of amino alcohols, depending on the amino

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alcohol structure, the solvent, the acyl donor and the nature of lipase used as biocatalyst.[14] For instance, Kanerva et al. have reported an effective acylation and deacylation via alcoholysis of 2-amino-1-phenylethanol derivatives using lipase *PS* and *CCL*.[15] On the other hand, the enzymatic deacylation via hydrolysis methodology has scarcely been reported for the preparation of optically active 2-amino cycloalkanols and 1,2-aminoindanols.[16] Honig et al. have reported the hydrolysis of 2′-substituted cyclohexylbutanoates by different commercially available lipases[17] and Takada et al. described enzymatic hydrolysis for the resolution of (±)-*trans*-2-substituted aminocyclohexanol by *Pseudomonas cepacia* lipase.[18] More recently, CAL-A has been successfully employed for the N-acylation of some β-aminoesters and the N-deacylation of their corresponding β-amidoesters.[19]

From the literature data, it can be seen that the conventional enzymatic hydrolysis protocols in biphasic media (water, buffer or water saturated) are limited by disadvantages including the decrease of the lipase's enantioselectivity due to the difficulty of controlling the pH value following the release of acetic acid of the aqueous solution, during the hydrolysis procedure.[20] Major constraints of aqueous media also include a slow solubility of the substrate and the liquid–liquid extraction step. Recently, we developed a highly enantioselective method for the deacylation of a set of benzylic acetates in a non-aqueous media catalyzed by CAL-B in the presence of sodium carbonate.[21] To extend the scope of this methodology, we have employed this procedure for the selective deprotection of *N*,*O*-protected amino alcohols.

Herein, the hydrolysis by alkaline-enzymatic kinetic resolution[21a] of *N*,*O*-protected amino alcohols in organic media is carried out. The efficiency of this process in terms of chemo- and enantioselectivity for the preparation of enantiomerically enriched 2-amino-1-arylethanols is described. Some aspects of the process are taken into consideration for developing a green and easy pathway via enzymatic hydrolysis in non-aqueous organic media in the presence of sodium carbonate.

## 2. Results and discussion

The amino alcohols selected herein are commercially available or easily synthesized from readily available starting material. The selected enzyme was the lipase from *Candida antarctica* fraction B (CAL-B), immobilized on an acrylic resin, with a specific activity >10,000 U/g; this choice was based on our previously investigations which show that only this lipase, present high reactivity and high enantioselectivities for this technique.[21a] Furthermore, a recent study shows that *Candida antarctica* lipase B is a chemoselective enzyme that preferentially catalyzes O-acylation over N-acylation.[22]

### 2.1. Enzymatic acylation of (*R*,*S*)-2-acetamide-1-phenylethanol 2a versus alkaline-enzymatic deacylation of 3a and 4a

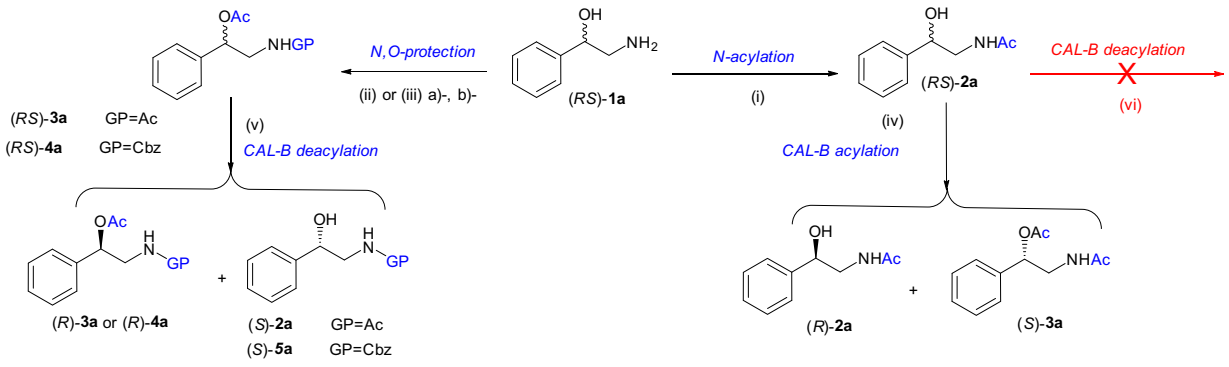
We examined the kinetic resolution catalyzed by CAL-B, the acylation and the hydrolysis, to compare the lipase performance using two complementary approaches (Scheme 1), and using 2-amino-1-phenyl ethanol as a model substrate. The mono-acyl derivative was prepared according to a recently described method[23] (Scheme 1i) and the bi-protected derivative by conventional organic methods (Scheme 1ii–iii).

We first carried out the enzymatic acylation reactions of the *N*-monoacylated substrate **2a**. Reactions were performed on 1 mmol of (*RS*)-**2a** with 3 mmol of acyl donor in the presence of a catalytic amount of lipase (CAL-B) in 3 mL of toluene (log*P* = 2.5) or diethyl ether (log*P* = 0.85) (Scheme 1iv). All reaction media were subjected to magnetic stirring at 40 °C for 24 h and the results are presented in Table 1.

The hydrolysis reactions were performed with an equimolecular ratio (1:1) of the protected amino alcohol (*RS*)-**2a** and $Na_2CO_3$, diluted in 3 mL of toluene, in the presence of 50 mg of CAL-B. The progress of the reactions is monitored by TLC. After 3 days of magnetic stirring at 40 °C, no progress was recorded. This indicated that CAL-B did not have the power to cleave the amide function under these conditions (Scheme 1vi).

We thus turned our attention to the O-deacylation of racemic *N*-protected-2-amino-1-phenylethyl acetates (Scheme 1v). The same experimental protocol was followed, and we studied the influence of the steric effect of the *N*-protecting group on the reactivity and selectivity of the enzymatic alkaline-hydrolysis of racemic **3a** and **4a**. The outcome of the reactions was monitored by chiral HPLC (Table 1).

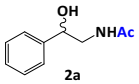
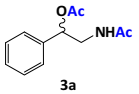
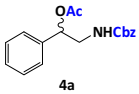
The results detailed in Table 1, show the low reactivity of CAL-B during the acylation of 2-acetamide-1-phenylethanol **2a**, with both acylating agents (entries 1–5). A very low selectivity was achieved for the kinetic resolutions carried out in $Et_2O$ ($E$ = 13, entry 1). Increasing the amount of enzyme slightly improved the conversion of the substrate, with both tested solvents (entry 1 vs 3 and entry 2 vs 4). Significant results in term of reactivity and selectivity were recorded with the hydrolysis of *N*,*O*-protected derivatives **3a**–**4a** catalyzed by CAL-B (50 mg) with sodium carbonate (1 mmol) in 3 mL toluene. Under these conditions, high chemo- and enantioselectivity were successfully achieved.



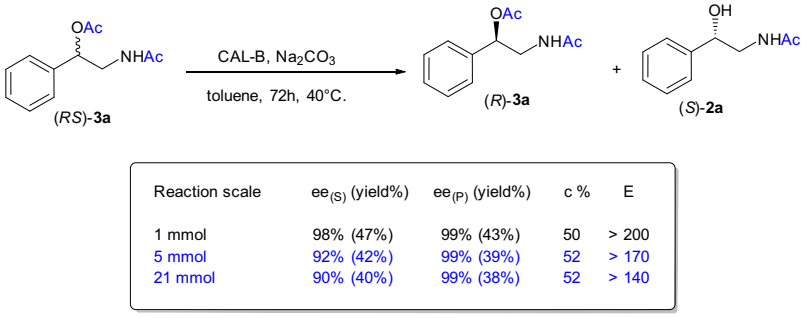

(i) Isopropenyl acetate, free solvent. (ii) Acetic anhydride, $CH_2Cl_2$. (iii)-a) NaOH 1M, $CH_2Cl_2$, CbzCl in toluene. (iii)-b) $CH_2Cl_2$, $Et_3N$, $Ac_2O$, DMAP. (iv) CAL-B, acyl donor, solvent, 24h, 40°C. (v) CAL-B, $Na_2CO_3$, toluene, 72h, 40°C.

**Scheme 1.** Complementary approaches for enzymatic kinetic resolution.

**Table 1**
Lipase acylation of **2a** versus deacylation of **3a**–**4a**

| Entry | Substrate | Nucleophile | CAL-B (mg) | Solvent | $ee_s$[d] (%) (*Conf.*)[h] | $ee_p$[d] (%) (*Conf.*)[h] | *c*[e] (%) | *E*[f] |
|---|---|---|---|---|---|---|---|---|
| 1[a] |  **2a** | Isopropenyl acetate | 20 | $Et_2O$ | 3 (*R*) | 86 (*S*) | 3 | 13 |
| 2[a] | | | 20 | Toluene | 2 (*R*) | 99 (*S*) | 2 | 200 |
| 3[a] | | | 50 | $Et_2O$ | 8 (*R*) | 90 (*S*) | 8 | 21 |
| 4[a] | | | 50 | Toluene | 9 (*R*) | 97 (*S*) | 8 | 72 |
| 5[a] | | Vinyl acetate | 50 | $Et_2O$ | 1 (*R*) | 30 (*S*) | 3 | 2 |
| 6[b] |  **3a** | $Na_2CO_3$ | 50 | Toluene | **57** (*R*) | **89** (*S*) | **39** | **>200** |
| 7[c] | | | 50 | Toluene | **99 (47)**[g] (*R*) | **98 (43)**[g] (*S*) | **50** | **>200** |
| 8[c] |  **4a** | | 50 | Toluene | **90 (45)**[g] (*R*) | **99 (48)**[g] (*S*) | **48** | **>200** |

[a] 1 mmol of (*RS*)-**2a**, 3 mmol of acyl donor in 3 mL of solvent in the presence of CAL-B for 24 h.
[b] 1 mmol of (*RS*)-**3a**, 1 mmol of $Na_2CO_3$ in 3 mL of toluene, 50 mg of CAL-B, for 24 h.
[c] 1 mmol of (*RS*)-**3a**, 1 mmol of $Na_2CO_3$ in 3 mL of toluene, 50 mg of CAL-B, for 72 h.
[d] Measured by chiral HPLC.
[e] Conversion:[24] $c = ee_s/ee_p + ee_s$.
[f] Selectivity:[24] $E = \ln[(1 - C)(1 - ee_s)]/\ln[(1 - C)(1 + ee_s)]$.
[g] Isolated yields.
[h] Absolute configuration measured and confirmed by literature data.




| Reaction scale | $ee_{(S)}$ (yield%) | $ee_{(P)}$ (yield%) | c % | E |
|---|---|---|---|---|
| 1 mmol | 98% (47%) | 99% (43%) | 50 | > 200 |
| 5 mmol | 92% (42%) | 99% (39%) | 52 | > 170 |
| 21 mmol | 90% (40%) | 99% (38%) | 52 | > 140 |

**Scheme 2.** Application of the kinetic resolution of (*RS*)-**3a** with CAL-B on a multigram scale.

This method allowed us to isolate both enantiomers of the starting materials and the deacylated products with excellent conversions 48% < *C* < 50% and high enantioselectivities (*E* >200) (entries 7–8). Furthermore, the steric hindrance of the *N*-protecting group does not affect the enantioselectivity and has very little effect on the conversion (entry 7 vs 8). The CAL-B enantiopreference for the (*S*)-enantiomer was confirmed and checked by a derivation of the commercially available (*R*)-2-amino-1-phenyl ethanol. The obtained (*R*)-2-acetamido-1-phenyl ethanol and (*R*)-2-acetamido-1-phenyl acetate was analyzed by chiral HPLC.

Considering the promising results obtained during the deacylation of 2-acetamide-1-phenylethyl acetate **3a**, we completed this investigation with a multigram scale reaction. Thus, a scaling up of the kinetic resolution was carried out starting from 1 g (5 mmol) to 4.7 g (21 mmol) of amido acetate **3a** in toluene, 1 equiv of $Na_2CO_3$ and an appropriate amount of CAL-B (Scheme 2).

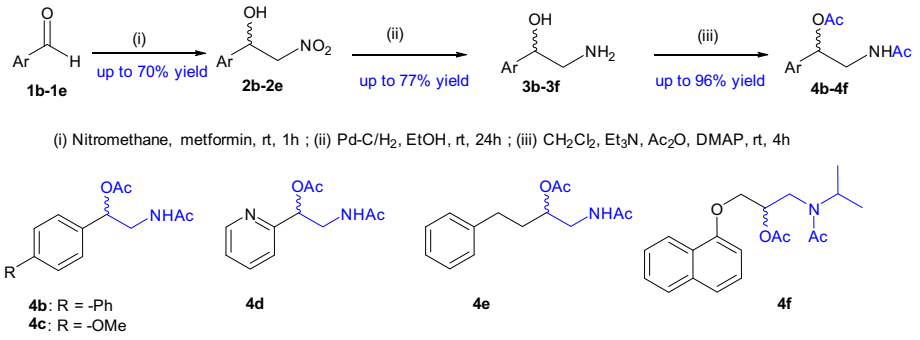
The quantitative yields were obtained regardless of the scale, with a conversion of *c* = 52% and a selectivity of *E* >140. The remaining enantiomer (*R*)-**3a** was isolated in 40% yield and with high enantiomeric excess (ee >99%) and the provided enantiomer (*S*)-**2a** in 38% yield and with 92% ee.

## 2.2. Alkaline enzymatic deacylation of some 2-acetamido-1-arylacetates

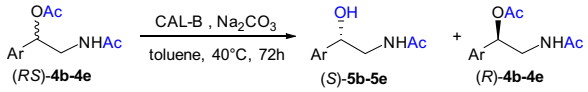
To study the scope of the CAL-B catalyzed hydrolysis in non-aqueous media by carbonate salts, we extended the methodology using our optimized conditions to other substrates **4b**–**4f**. It should be noted that to the best of our knowledge the enzymatic hydrolysis has never been reported previously, in either conventional or non-conventional media. The racemic 2-acetamido-1-arylacetates **4b**–**4e** were synthesized, in good overall chemical yields in three steps from the corresponding aldehydes following a modified synthesis protocol (Scheme 3) that incorporates easy and soft pathways.[25]

β-Nitro-alcohols **2b**–**2e** were obtained by coupling the corresponding aldehydes **1b**–**1e** with nitromethane in the presence of a catalytic amount of metformin (5 mol %), without a solvent, at room temperature according to the modified Henry reaction.[26] They are obtained with chemical yields between 70% and 88%. Racemic β-amino alcohols **3b**–**3e** were obtained by the reduction of the corresponding β-nitro-alcohols using Pd/C under an atmosphere of $H_2$,[27] and were recovered with isolated chemical yields between 86% and 95% yield.

Finally, 2-acetamido-1-aryl acetates **4b**–**4e** were quantitatively obtained by chemical acylation of the β-amino alcohols **3b**–**3e** using acetic anhydride (>96% yield). Following the same acylation procedure, the *N*-acetylamino-acetate **4f** was recovered with yield of 54% directly from the commercially propranolol **3f**. The kinetic resolution via enzymatic hydrolysis in non-conventional media using sodium carbonate was applied to the synthesized (*RS*)-**4b**–**4f** compounds. The reactions were carried out using optimized conditions described in Table 1. The reaction mixture was stirred magnetically at 40 °C for 72 h (Scheme 4).




**Scheme 3.** General synthetic route to 2-acetamido-1-aryl acetates.




**Scheme 4.** Kinetic resolution via enzymatic hydrolysis of **4b**–**4e** with $Na_2CO_3$.

The progress of the reaction and the enantiomeric excess of the residual substrate and the *N*-monoacylated were determined by high performance liquid chromatography. The results are summarized in Table 2.

The results of Table 2 show the significant influence of the structure of 2-acetamido-1-aryl acetates on the reactivity and selectivity of the CAL-B during their hydrolysis in the presence of sodium carbonate. The highest enantiomeric excess was recorded for the resolution of (*RS*)-**4d**, the kinetic resolution is highly selective with a conversion of $c = 50\%$ and a selectivity of $E > 200$.

The enantiomers (product and substrate) were obtained with high enantiomeric purity >99% ee, the presence of the pyridine moiety intervenes favorably to the enantioselection by CAL-B under those conditions (entry 3). CAL-B showed a very good affinity during the hydrolysis of this substrate. Selectivity was also very high for **4c** ($E > 200$) with a small decrease of the conversion $c = 33\%$. This phenomenon can be attributed to the presence of methoxy substituent at the *para*-position of the aromatic ring. The oxygen or azote atom, with its high electronegativity, can inductively withdraw electrons through sigma –bonds and so should be taken into account.[28]

For the other hydrolyzed substrates, CAL-B retained its reactivity; the conversions obtained for **4b** and **4e** were $c = 34\%$ and $c = 57\%$, respectively (entries 1 and 4), with drastic loss of enantioselectivity ($E < 8$). Finally, with propranolol, the rate of progress of the hydrolysis did not exceed the 20% without an enantiopreference (entry 5). These outcomes can be attributed to the inductive effects negatively distressing the enantioselection for compound **4b**, but in the case of **4e** and **4f**, it is more because of the remoteness of the stereogenic center that impacts negatively on selectivity.

## 3. Conclusion

We have developed a new and efficient route to access enantiomerically pure β-amino alcohols via alkaline hydrolysis under hydrophobic organic media using CAL-B as biocatalysts. This allows direct access to a number of interesting building blocks with high enantiomeric excesses. The enantioenriched β-amino alcohols derivatives were obtained by chemo- and enantioselective pathways promoted by CAL-B catalyzed hydrolysis and assisted by sodium carbonate in toluene. CAL-B shows a very interesting selective activity with the enantioselective cleavage of *O*-acetyl group.

The synthesis of racemic β-amino alcohols was carried out via a modified Henry reaction, catalyzed by a super organic base: metformin, and the products were obtained with good chemical yields (yield >80%) using a simpler and greener synthesis. A novel hydrolysis process in toluene with sodium carbonate catalyzed by CAL-B has been successfully extended to a set of 2-amino-1-arylethanol derivatives **3a**, **4a**, **4c**, and **4d**. The substitution of the aromatic ring by electron withdrawing groups and the remoteness of the stereogenic center cause a drop in reactivity and selectivity, while the aromaticity (phenyl or pyridyl group) is in favor of the enantiomer (*S*)-mono acylated by CAL-B (ee up to 99%). We have also devised a straightforward and high yield preparation of both enantiomers of 1,2-amino phenylethanol, which be easily prepared on a large scale and is useful for further transformations.

## 4. Experimental

### 4.1. General

All reagents purchased from either Aldrich, Acros, TCI or Alfa Aesar and were used as received. The *Candida antarctica lipase*

**Table 2**
CAL-B-catalyzed hydrolysis of **4a**–**4f** with $Na_2CO_3$

| Entry[a] | Substrate | $ee_s$[b] (%) (*Conf.*)[f] | Yield[c] (%) | $ee_p$[b] (%) (*Conf.*)[f] | Yield[c] (%) | *c*[d] (%) | *E*[e] |
|---|---|---|---|---|---|---|---|
| 1 | **4b** | 36 (*R*) | 64 | 69 (*S*) | 35 | 34 | 8 |
| 2 | **4c** | **49** (*R*) | **50** | **97** (*S*) | **30** | **33** | **>200** |
| 3 | **4d** | **>99** (*R*) | **44** | **>99** (*S*) | **40** | **50** | **>200** |
| 4 | **4e** | 48 (*R*) | 60 | 35 (*S*) | 30 | 57 | 3 |
| 5 | **4f** | 3 | 83 | 12 | 12 | 20 | 1 |

[a] 1 mmol of racemic *N*-acetyl-aminoacetate, 1 mmol of $Na_2CO_3$ in 3 mL of toluene in the presence of 50 mg of CAL-B for 72 h.
[b] Measured by chiral HPLC.
[c] Isolated yields.
[d] Conversion:[24] $c = ee_s/ee_p + ee_s$.
[e] Selectivity:[24] $E = \ln[(1 - C)(1 - ee_s)]/\ln[(1 - C)(1 + ee_s)]$.
[f] Sign of $[\alpha]_D^{20}$.

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 and ninhydrin solution and heat as developing agents.

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 $CDCl_3$; peak at 4.87 ppm in $^1H$ NMR and 7 peaks at 49 ppm in $^{13}C$ NMR in the case of $CD_3OD$). The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = double-doublet, ddd = double-double-doublet, td = triple-doublet, qd = quartet-doublets. Chemical shifts are expressed in ppm and coupling constant ($J$) in Hz. The enantiomeric excesses were measured by a chiral stationary phase HPLC on Chiralpak®AD-H (4.6 × 250 mm), Chiralpak®IC (4.6 × 250 mm) and Chiralpak®IA (4.6 × 250 mm) column. Retention times are reported in minutes. Optical rotations were determined using a Perkin-Elmer 241 Polarimeter at room temperature using a cell of 1 dm length and $\lambda$ = 589 nm.

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

#### 4.2.1. Preparation of (*RS*)-2-acetamide-1-phenylethanol 2a

A mixture of 2-amino-1-phenylethanol **1a** (1 mmol, 0.137 g) and isopropenyl acetate (3 mmol, 0.300 g) were stirred at room temperature for 24 h until complete consumption of the amino alcohol. The excess isopropenyl acetate was then eliminated under reduced pressure. Acetamide **2a** was obtained quantitatively without purification, as a white powder (0.179 g, >99%). $R_f$ = 0.57 ($CH_2Cl_2$/Acetone: 50/50). $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 1.9 (s, 3H), 3.3 (dd, $J$ = 7.6 and 5.9 Hz, 1H), 3.4 (dd, $J$ = 13.6, 4.6 Hz, 1H), 4.7 (dd, $J$ = 8.0, 4.6 Hz, 1H), 7.2–7.4 (m, 5H). $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta$ 172.5, 142.8, 128.2, 127.5, 126.0, 72.4, 21.4.

#### 4.2.2. General procedures for the synthesis of racemic amino alcohols 3b–3e

**4.2.2.1. General synthesis of nitroalcohols 2b–2e.** *4.2.2.1.1. Preparation of free metformin.* To a solution of NaOH (40 mg, 1 mmol) and ethanol (5 mL) was added metformin hydrochloride (165.5 mg, 1 mmol) and the resulting suspension was stirred for 1 h at room temperature. The recovered suspension was filtered, and ethanol was removed from the filtrate with rotary evaporation leading to free metformin in 99% yield. The obtained free metformin was freshly used in the next experiments. A mixture of the aldehyde (1 mmol), nitromethane (2 mmol) and metformin (5 mol %) was stirred at room temperature for 1 h. The reaction was monitored by NMR. After total consumption of the aldehyde, the reaction mixture was well-washed using distilled water and evaporated to give the appropriate β-nitroalcohol. The $^1H$ and $^{13}C$ NMR spectra of the β-nitroalcohols were in good agreement with the literature.

*4.2.2.1.2. 1-([1,1′-Biphenyl]-4-yl)-2-nitroethanol **2b**.* Yield: 88%; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.9 (br s, 1H), 4.6 (qd, $J$ = 13.3, 6.3 Hz, 2H), 5.52 (dd, $J$ = 9.3, 2.7 Hz, 1H), 7.3–7.4 (m, 5H), 7.5–7.6 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 142, 140.3, 137, 129, 127.8, 127.8, 127.2, 126.5, 81.2, 70.9.

*4.2.2.1.3. 1-(4-Methoxyphenyl)-2-nitroethanol **2c**.* Yield: 70%; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.79 (br s, 1H), 3.8 (s, 3H), 4.4 (dd, $J$ = 13.2, 3.2 Hz, 1H), 4.5 (dd, $J$ = 13.2, 9.6 Hz, 1H), 5.3 (dd, $J$ = 9.5, 3.2 Hz, 1H), 6.9–6.9 (m, 2H), 7.3–7.3 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 55.4, 70.7, 81.3, 114.5, 127.4, 130.3, 160.1.

*4.2.2.1.4. 2-Nitro-1-(pyridin-2-yl)ethanol **2d**.* Yield: 70%; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.3 (br s, 1H), 4.6 (dd, $J$ = 13.0, 8.5 Hz, 1H), 4.7 (dd, $J$ = 13.0, 3.6 Hz, 1H), 5.4 (dd, $J$ = 8.5, 3.6 Hz, 1H), 7.3 (ddd, $J$ = 7.6, 4.9, 0.8 Hz, 1H), 7.4 (dd, $J$ = 7.9, 0.5 Hz, 1H), 7.7 (td, $J$ = 7.7, 1.7 Hz, 1H), 8.5 (ddd, $J$ = 4.8, 1.4, 0.9 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 156.6, 149, 137.6, 123.7, 121, 80.8, 70.4.

*4.2.2.1.5. 1-Nitro-4-phenylbutan-2-ol **2e**.* Yield: 88%; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.7–1.9 (m, 2H), 2.6–2.7 (m, 1H), 2.7–2.9 (m, 2H), 4.2–4.3 (m, 1H), 4.3–4.4 (m, 2H), 7.2–7.25 (m, 3H), 7.29–7.35 (m, 2H).

#### 4.2.3. General procedure for the reduction of β-nitroalcohols 3b–3e

In a round bottom flask, the β-nitroalcohol (1 mmol) was dissolved in 5 mL of ethanol and charged with a catalytic amount of palladium on activated carbon (10 mol %). The reaction vessel was evacuated and aerated with hydrogen gas. The reaction mixture was stirred at room temperature for 24 h. The solution was then filtered through a pad of Celite and evaporated to dryness. The $^1H$ and $^{13}C$ NMR spectra of the β-amino alcohols were in good agreement with the literature.

**4.2.3.1. 1-([1,1′-Biphenyl]-4-yl)-2-aminoethanol 3b.** Yield: 95%; $R_f$ = 0.09 ($CH_2Cl_2$/Acetone: 50/50). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.9 (br s, 2H), 2.8 (dd, $J$ = 12.6, 7.8 Hz, 1H), 3 (dd, $J$ = 12.5, 4.0 Hz, 1H), 4.6 (q, $J$ = 4.0 Hz, 1H), 7.32–7.37 (m, 1H), 7.42–7.46 (m, 4H), 7.58 (d, $J$ = 8.1 Hz, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 141.6, 141, 140.6, 128.9, 127.4, 127.3, 127.2, 126.4, 74.2, 49.3.

**4.2.3.2. 2-Amino-1-(4-methoxyphenyl)ethanol 3c.** Yield: 92%; $R_f$ = 0.08 ($CH_2Cl_2$/Acetone: 50/50). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.5 (br s, 2H), 2.8 (dd, $J$ = 12.7, 7.9 Hz, 1H), 2.9 (dd, $J$ = 12.4, 4.1 Hz, 1H), 3.8 (s, 3H), 4.6 (dd, $J$ = 7.9, 4.0 Hz, 1H), 6.89–6.91 (m, 2H), 7.27–7.3 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 159.1, 134.7, 127.2, 113.8, 73.9, 55.3, 49.3.

**4.2.3.3. 2-Amino-1-(pyridin-2-yl)ethanol 3d.** Yield: 92%; $R_f$ = 0.06 ($CH_2Cl_2$/Acetone: 30/70). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.8 (d, $J$ = 6.6 Hz, 2H), 2.8 (d, $J$ = 6.6 Hz, 1H), 3 (dd, $J$ = 13.1, 3.8 Hz, 1H), 4.6 (dd, $J$ = 6.6, 3.8 Hz, 1H), 7.1 (ddd, $J$ = 7.5, 4.9, 0.9 Hz, 1H), 7.3 (d, $J$ = 7.9 Hz, 1H), 7.6 (td, $J$ = 7.7, 1.8 Hz, 1H), 8.4 (ddd, $J$ = 4.8, 1.5, 0.9 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 160.7, 148.4, 136.8, 122.4, 120.5, 73.9, 48.5.

**4.2.3.4. 1-Amino-4-phenylbutan-2-ol 3e.** Yield: 86%; $R_f$ = 0.14 ($CH_2Cl_2$/Acetone: 60/40). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.7–1.8 (m, 2H), 2.50 (s, 2H), 2.6 (dd, $J$ = 12.6, 8.4 Hz, 1H), 2.7–2.8 (m, 1H), 2.9 (ddd, $J$ = 12.8, 8.5, 4.9 Hz, 2H), 3.5–3.6 (m, 1H), 7.3 (dd, $J$ = 7.6, 3.0 Hz, 3H), 7.3–7.4 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 142.1, 128.5, 128.4, 125.8, 71.1, 47.5, 36.5, 32.

#### 4.2.4. Synthesis of (*RS*)-2-(((benzyloxy)carbonyl)amino)-1-phenylethyl acetate 4a

To a solution of **1a** (2 mmol, 0.274 g) in 2 mL of $CH_2Cl_2$ was added a solution of NaOH 1 M (2 mL) and the mixture was cooled to 0 °C. To the mixture, 50% of benzyl chloroformate in toluene (2 mmol) was added and the reaction was stirred at room temperature for 16 h. The reaction crude was washed with $H_2O$ and the organic phases were combined, dried over $MgSO_4$ and evaporated under reduced pressure to give 0.5 g of a white solid (92% isolated yield). To a solution of this product in 2 mL of $CH_2Cl_2$ were added, successively, 2 equiv of anhydride acetic, 2 equiv of $Et_3N$, and a catalytic amount of 4-dimethylaminopyridine (0.2 equiv). The final product **4a** was obtained pure after standard work-up in yield >99%. $R_f$ = 0.5. (Petroleum ether/AcOEt: 70/30). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2 (s, 3H), 2.2 (s, 2H), 3.4–3.6 (m, 2H), 5.1 (br

s, 1H), 5.8 (dd, $J$ = 7.8, 4.4 Hz, 1H), 7.2–7.3 (m, 10H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.1, 166.4, 137.6, 136.4, 128.6, 128.5, 128.4, 128.1, 126.4, 66.8, 45.8, 22.1, 21.

#### 4.2.5. General procedure for the synthesis of racemic β-*N*-acetyl-aminoacetate 3a, 4b–4f

The *N*-acetyl-aminoacetates were synthesized by classical chemical acylation via the corresponding racemic β-amino 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 $CH_2Cl_2$. The final products were obtained pure after standard work-up in excellent yields. The $^1$H and $^{13}$C NMR spectra of these products were in good agreement with the literature.

**4.2.5.1. 2-Acetamido-1-phenylethyl acetate 3a.** Yield: >99%; $R_f$ = 0.79 ($CH_2Cl_2$/Acetone: 50/50). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.9 (s, 3H), 2 (s, 3H), 3.5 (ddd, $J$ = 14.0, 8.2, 5.6 Hz, 1H), 3.6 (ddd, $J$ = 14.0, 6.2, 4.4 Hz, 1H), 5.8 (dd, $J$ = 8.2, 4.4 Hz, 1H), 7.2–7.3 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.4, 170.2, 137.7, 128.5, 128.3, 126.3, 74.4, 44.3, 22.9, 21.

**4.2.5.2. 1-([1,1′-Viphenyl]-4-yl)-2-acetamidoethyl acetate 4b.** Yield: >99%; $R_f$ = 0.84. ($CH_2Cl_2$/Acetone: 60/40). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.9 (s, 3H), 2.1 (s, 3H), 3.5–3.7 (m, 2H), 5.8 (q, $J$ = 4.4 Hz, 1H), 7.35–7.38 (m, 1H), 7.40–7.47 (m, 4H), 7.55–7.6 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.4, 170.2, 141.4, 140.4, 136.6, 128.8, 127.5, 127.4, 127.1, 126.9, 74.4, 44.3, 23.2, 21.2.

**4.2.5.3. 2-Acetamido-1-(4-methoxyphenyl)ethyl acetate 4c.** Yield: >99%; $R_f$ = 0.63. ($CH_2Cl_2$/Acetone: 60/40). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.9 (s, 3H), 2 (s, 3H), 3.4–3.6 (m, 3H), 3.7 (s, 3H), 5.7 (dd, $J$ = 8.0, 4.8 Hz, 1H), 6 (br s, 1H), 6.82–6.87 (m, 2H), 7.21–7.25 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.5, 170.2, 159.7, 129.8, 128, 114.1, 74.3, 55.3, 44.3, 23.3, 21.3.

**4.2.5.4. 2-Acetamido-1-(pyridin-2-yl)ethyl acetate 4d.** Yield: 96%; $R_f$ = 0.57. ($CH_2Cl_2$/Acetone: 30/70). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.9 (s, 3H), 2.1 (s, 3H), 3.6–3.7 (m, 1H), 3.8–3.9 (m, 1H), 5.8 (dd, $J$ = 6.4, 4.9 Hz, 1H), 6.2 (br s, 1H), 7.2 (ddd, $J$ = 7.6, 4.9, 1.1 Hz, 1H), 7.3 (d, $J$ = 7.9 Hz, 1H), 7.6 (td, $J$ = 7.7, 1.8 Hz, 1H), 8.5 (ddd, $J$ = 4.9, 1.6, 0.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.3, 170.3, 156.9, 149.2, 136.9, 134.6, 123.2, 122, 74.3, 42.6, 23.2, 21.

**4.2.5.5. 1-Acetamido-4-phenylbutan-2-yl acetate 4e.** Yield: >99%; $R_f$ = 0.41. ($CH_2Cl_2$/Acetone: 60/40). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.80–1.9 (m, 2H), 1.9 (s, 3H), 2 (s, 3H), 2.5–2.7 (m, 2H), 3.3–3.4 (m, 2H), 4.90–4.95 (m, 1H), 5.9 (br s, 1H), 7.14–7.19 (m, 3H), 7.28 (m, 2H).

**4.2.5.6. 1-(*N*-Isopropylacetamido)-3-(naphthalen-1-yloxy)propan-2-yl acetate 4f.** Yield: 54%; $R_f$ = 0.88 ($CH_2Cl_2$/Acetone: 90/10). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.2–1.36 (m, 6H), 2–2.24 (m, 6H), 3.4 (dd, $J$ = 14.3, 6.9 Hz, 1H), 3.8–3.89 (m, 1H), 4 (dt, $J$ = 13.4, 6.7 Hz, 1H), 4.3 (ddd, $J$ = 16.9, 10.7, 3.9 Hz, 2H), 5.4–5.7 (m, 1H), 6.8 (dd, $J$ = 16.2, 7.2 Hz, 1H), 7.3–7.5 (m, 4H), 7.7–7.8 (m, 1H), 8.2 (dd, $J$ = 8.3, 5.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.3, 170.6, 154.3, 134.5, 127.7, 127.5, 126.4, 125.9, 125.3, 121.9, 120.6, 104.9, 71.7, 68.4, 49.6, 41.4, 22.2, 21.8, 21.2, 21.

### 4.3. Enzymatic kinetic resolutions procedures

#### 4.3.1. Enzymatic acylation of 2a

All enzymatic acylation reactions were performed using 1 equiv of (*RS*)-2-acetamide-1-phenylethanol **2a** (1 mmol, 0.179 g) and 3 equiv of the appropriate acetyl donor dissolved in 3 mL of solvent. A catalytic amount of CAL-B was added and the mixture was shaken at 40 °C for 24 h. After removal of the enzyme by filtration and evaporation of the solvent, the reaction mixture was analyzed by chiral HPLC.

#### 4.3.2. General procedure for the enzymatic hydrolysis of racemic β-*N*-protected-aminoacetate 3a, 4a–4f

In a typical procedure, 1 mmol of racemic β-*N*-protected-aminoacetates **3a**, **4a**–**4f** is dissolved in 3 mL of toluene before the addition of 1 mmol of sodium carbonate and 50 mg of CAL-B. The mixture was stirred 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 ($CH_2Cl_2$/EtOAc: with different fraction) to separate the residual (*R*)-*N*-protected-aminoacetate and the furnished (*S*)-*N*-protected-amino alcohol. The two optically active compounds were analysed by chiral HPLC.

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## A. Supplementary data

Supplementary data (all experimental procedures; characterization spectra (NMR and chiral chromatography) of all synthesized products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.10.003.

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