

Enzymatic Kinetic Resolution of Tertiary Benzyl Bicyclic Alcohols: Studies of the Reaction Conditions for a More Efficient Protocol

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The reactivity and steric hindrance of optically active tertiary alcohols limit the development of more direct enantioselective methodologies for their synthesis, such as kinetic resolution (KR). In this work, we optimized the reaction conditions of an enzymatic KR of two tertiary benzyl bicyclic alcohols using readily available reagents and biocatalyst. Studies were conducted with 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol and 1-methyl-2,3-dihydro-1*H*-inden-1-ol as substrates and commercial lipase A from *Candida antarctica* (CAL-A) as biocatalyst for the enantioselective transesterification of these racemic tertiary alcohols. After varying the reaction parameters, such as acyl donor, solvent, and enzyme/substrate ratio, the (*R*)-esters were obtained with high conversions (44-45%) and excellent enantiomeric excess (96-99%) in only 4-5 h, to our knowledge being the best result for KR of the evaluated tertiary alcohols in terms of reaction rate, conversion, and enantioselectivity reported so far.

Keywords: tertiary alcohol, kinetic resolution, lipase, enantioselective transesterification

Introduction

Optically active tertiary alcohols are important synthons for the pharmaceutical and fine chemical industries.^{1,2} Due to their steric nature, chiral tertiary alcohols are also used extensively as ligands or auxiliaries in asymmetric synthesis.³ Thus, there is enormous demand for enantioselective methods for preparing tertiary alcohols, and the challenges in this field are considerable. For example, the addition of carbon nucleophiles to prochiral ketones using organometallic reagents, one of the most common and direct methods, usually faces problems, including low precursor reactivity and poor enantiofacial differentiation.^{1,4} Extensive efforts have been made toward developing optimized nucleophilic addition protocols,¹ but most approaches require activated ketones, such as α -ketoesters and α -CF₃ ketones, which are difficult to combine with highly reactive organometallic reagents.⁵

An attractive alternative to preparing optically active tertiary alcohols is to start from readily available racemic tertiary alcohols. Catalytic kinetic resolution (KR) resolves a racemic mixture by converting one of the enantiomers

to an enantiopure product at a higher reaction rate in the presence of a chiral catalyst, achieving up to 50% yield.⁶⁻⁸ The chiral catalyst must show greater structural complementarity with one of the enantiomers (chiral recognition).⁸ Although enzymatic and non-enzymatic catalytic methods are widely used in KR of secondary alcohols, KR of tertiary alcohols is still tricky.⁶ A significant problem is finding a chiral catalyst that recognizes three non-hydrogen substituents at the α -position of tertiary alcohols. Furthermore, side reactions, such as dehydration and elimination, limit the development of KR methods.⁵

Recent KR methods for tertiary alcohols generally involve chemical catalysts and functionalized substrates, as illustrated in the reviews of Chen *et al.*⁵ and Ding *et al.*⁶ Despite the excellent advances achieved by these recent works, the direct KR of the OH group from the quaternary center without adjacent reactive substituents is still a remarkable obstacle.

Enzymes can be used as catalysts to overcome this problem because these biomolecules can achieve high chemo-, regio-, and enantioselectivities in milder reaction conditions.⁹ For example, hydrolases such as esterases and lipases are commonly used as biocatalysts in KR protocols for secondary alcohols and amines via enantioselective acylation or hydrolysis of their corresponding esters or

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amides.³ However, due to the limitation that only unique hydrolases have a specific active site to accommodate sterically hindered tertiary alcohols, there are few examples of enzymatic KR with high conversion and enantiomeric excess (*ee*) values, and most of them involve the hydrolysis of esters from tertiary benzylic propargylic alcohols catalyzed by variants of hydrolases obtained by protein engineering.^{10–19}

Nevertheless, KR protocols catalyzed by hydrolases in organic media can facilitate the isolation of the resolution products and overcome the autohydrolysis of esters from tertiary alcohols mentioned in previous works.^{10,12,15} In this approach, lipase A from *Candida antarctica* (CAL-A) showed the best activity and enantioselectivity towards tertiary alcohols, especially when immobilized.^{10,14,18–21} However, these previous works have limitations in terms of cost-effectiveness, such as prolonged reaction time (between 48 and 120 h),^{10,14,18–21} usage of a high enzyme loading (for example, 137:1 of enzyme/substrate ratio)¹⁰ or the need to resort to protein engineering.¹⁹ Furthermore, most of these studies of enzymatic KR in organic media have explored the tertiary benzylic propargylic alcohols as substrates.

In particular, the search for efficient methods to obtain optically active tertiary alcohols of ketones such as α -tetralone and α -indanone is of great importance since tetralones and indanones derivatives showed a broad spectrum of biological activities, and these moieties are considered privileged scaffolds in chemical and pharmaceutical industries.^{22,23} To our knowledge, there are only two works of enzymatic KR of tertiary alcohols of α -tetralone and α -indanone.^{14,20} In both studies, the wild-type and immobilized CAL-A promoted the KR in organic media via transesterification with vinyl acetate as an acyl donor.

In 2008, Özdemirhan *et al.*¹⁴ achieved the KR of 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (*rac*-**1a**) with 25% of conversion into the (*R*)-ester (91% *ee*) in 48 h, while the result for the five-membered ring 1-methyl-2,3-dihydro-1*H*-inden-1-ol (*rac*-**1b**) was 20% of conversion and 71% *ee* in 72 h, using CAL-A immobilized via cross-linked enzyme aggregate (CLEA). In 2020, Kühn *et al.*²⁰ reported the

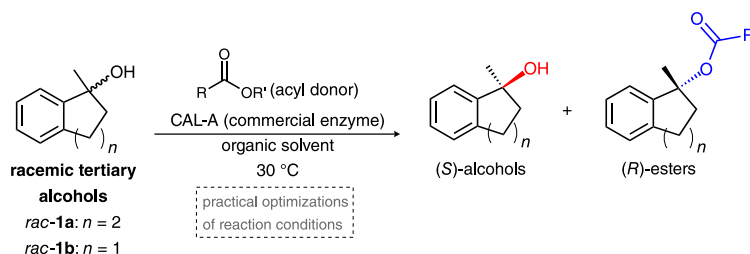
KR of *rac*-**1a** using the commercial immobilized CAL-A adsorbed on Immobead-150, achieving conversion to the (*R*)-ester of 32% (> 99% *ee*) in 48 h. They also extended the methodology to a dynamic process for the first time, combining the KR step catalyzed by CAL-A with *in situ* acid racemization catalysed by an oxovanadium catalyst. After sequentially adding of both catalysts in tailor-made portions over 13 days, they obtained the optically active (*R*)-product **2a** with 77% yield and 99% *ee* without side-product formation.²⁰ Unfortunately, the protocol did not apply to other substrates, and the authors mentioned that the stability of the alcohol *rac*-**1b** and its corresponding acetate was difficult due to their decomposition into elimination products.²⁰

We believe that further studies of the reaction conditions of the lipase-catalyzed KR of tertiary benzyl bicyclic alcohols derived from α -tetralone and α -indanone can provide more practical and efficient resolution methods for these challenging substrates. Herein, we report our efforts toward an optimized KR of the tertiary benzyl bicyclic alcohols 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (*rac*-**1a**) and 1-methyl-2,3-dihydro-1*H*-inden-1-ol (*rac*-**1b**) catalyzed by the commercial immobilized CAL-A to meet the demand for KR protocols for tertiary alcohols with greater applicability and cost-effectiveness (Scheme 1).

Experimental

General information

1-Indanone (> 99%), methylmagnesium bromide solution (3.0 M in diethyl ether), acyl donors vinyl acetate, isopropenyl acetate, ethyl acetate, ethyl trifluoroacetate and vinyl butyrate, and immobilized CAL-A (≥ 500 U g⁻¹, recombinant, expressed in *Aspergillus oryzae* and adsorbed on Immobead-150) were purchased from Sigma-Aldrich (St. Louis, MO, USA). 1-Tetralone (97%) was obtained from Oakwood Chemical (Estill, SC, USA). Racemic alcohols 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (*rac*-**1a**) and 1-methyl-2,3-dihydro-1*H*-inden-1-ol (*rac*-**1b**) were synthesized via Grignard reactions following a previously described procedure.²⁴ Racemic esters



Scheme 1. Enzymatic kinetic resolution (KR) of tertiary benzyl bicyclic alcohols studied in this work (CAL-A: lipase A from *Candida antarctica*).

were synthesized for use as references for the gas chromatography-flame ionization detection (GC-FID) analysis, by 4-dimethylaminopyridine (DMAP)-catalyzed esterifications of corresponding alcohols **1a** and **1b** in triethylamine as solvent. The Supplementary Information (SI) section provides details of the procedures and the full characterization data for the synthesized compounds.

GC-FID analysis was performed on a gas chromatograph (GC-2010 Plus, Shimadzu, Kyoto, Japan) equipped with an autosampler (AOC-20i, Shimadzu, Kyoto, Japan) using hydrogen as the carrier gas (1 mL min⁻¹). To determine the conversion values, a (5%-phenyl)-methylpolysiloxane column (J&W HP-5-ms, Agilent, Santa Clara, CA, United States) was used with injector and interface temperatures of 260 and 280 °C, respectively. For all analyses with HP-5-ms column, the temperature program was as follows: 80 °C for 3 min; increased to 280 °C at 30 °C min⁻¹; and held for 10 min. The conversion percentages were calculated by comparing the estimated concentration of (*R*)-esters in the reaction mixture aliquots (determined by using a 8-point calibration curve with *n*-tetradecane (0.025 mmol mL⁻¹) as the internal standard and the corresponding racemic esters as analytes) and the expected concentration of these compounds for a 50%-conversion KR under the applied reaction conditions. The *ee* values were determined with a chiral column (J&W CP-Chirasil-DEX CB, Agilent; 25 m × 0.25 mm × 0.25 μm, Santa Clara, CA, United States) and using the relative peak areas of each enantiomer. The *ee* percentages were calculated following the equation: $ee\ (\%) = [(A_{\text{major}} - A_{\text{minor}})] / [(A_{\text{major}} + A_{\text{minor}})] \times 100$, where A_{major} and A_{minor} are, respectively, the relative peak areas of the major and minor enantiomers of the chiral compounds in the chromatograms. For all analyses with CP-Chirasil-DEX CB column, the injector and interface temperatures were 160 and 180 °C, respectively, and the temperature program was as follows: 100 °C for 3 min; increased to 140 °C at 5 °C min⁻¹; held at 140 °C for 5 min; increased to 180 °C at 10 °C min⁻¹; and held for 15 min.

Enantioselectivity (*E*-value) was determined by the following equation: $E = \ln[(1 - c) \times (1 + ee_p)] / \ln[(1 - c) \times (1 - ee_p)]$, where *c* is conversion and *ee_p* is the enantiomeric excess of the (*R*)-esters (KR products).

Gas chromatography-mass spectrometry (GC-MS) analysis was performed on a gas chromatograph (7890B, Agilent, Santa Clara, CA, United States) coupled to a mass spectrometer (5977A, Agilent, Santa Clara, CA, United States) with electron impact ionization at 70 eV, a (5%-phenyl)-methylpolysiloxane column (J&W HP-5-ms, Agilent; 30 m × 0.25 mm ID, Santa Clara, CA, United States), and helium as the carrier gas (1 mL min⁻¹). The injector and interface temperatures were 260 and

280 °C, respectively. The GC-MS temperature program was as follows: 80 °C for 3 min; increased to 280 °C at 30 °C min⁻¹; and held for 5 min.

Column chromatography was performed on aluminium oxide 90 active neutral (70-230 Mesh ASTM, Merck Millipore, Darmstadt, Germany). Infrared spectra were acquired on a spectrometer (Vertex 70v FTIR, Bruker, Billerica, MA, USA) using diamond crystal attenuated total reflection (ATR) in a wavenumber range of 400 to 4000 cm⁻¹. Optical rotations were measured in CHCl₃ solutions at 25-26 °C on a polarimeter (341 LC, PerkinElmer, Shelton, CT, USA) at the sodium D line (589 nm) and with a 1.00 dm quartz cell.

¹H and ¹³C nuclear magnetic resonance (NMR) spectra were acquired on a spectrometer AVANCE III HD 600 (Bruker; B₀ 14.1 T, Billerica, MA, USA) operating at a frequency of 600.13 MHz for the ¹H nucleus and 150.90 MHz for the ¹³C nucleus or on a spectrometer Fourier 300 (Bruker; B₀ 7.1 T, Billerica, MA, USA) operating at a frequency of 300.19 MHz for the ¹H nucleus and 75.48 MHz for the ¹³C nucleus. Chemical shifts were expressed in ppm downfield from tetramethylsilane (TMS) and CDCl₃ was used as the solvent.

General procedure for KR reactions

Tertiary alcohol *rac*-**1a** (0.16 mmol, 26 mg) and an acyl donor (10 equiv, 1.60 mmol) were added to a 25-mL two-neck round bottom flask. After complete solubilization of the alcohol, 1:1 m/m of CAL-A (enzyme/substrate ratio, 26 mg) and organic solvent (2.0 mL) were added to the solution. The resulting suspensions were stirred at 30 °C with a magnetic bar, and the reactions were monitored by GC-FID. After reaching maximum substrate conversions to the (*R*)-products and lower side-product formation, the enzyme was removed with a filter paper and washed with ethyl acetate (2 × 2.0 mL), and the result solutions were concentrated under reduced pressure. Aliquots of the result crude product were prepared with the addition of *n*-tetradecane (0.025 mmol mL⁻¹, solution in ethyl acetate HPLC grade) for determination of (*R*)-products concentration by GC-FID. This procedure was performed using different acyl donors (vinyl acetate, isopropenyl acetate, ethyl acetate, ethyl trifluoroacetate and vinyl butyrate), solvents (diisopropyl ether, acetonitrile, trifluorotoluene, heptane and isooctane) and enzyme amounts (26, 52 and 78 mg). The described procedure was also performed using *rac*-**1b** (0.16 mmol, 21 mg) as substrate and the following reaction conditions: vinyl butyrate (10 equiv, 1.60 mmol, 183 mg), 2:1 m/m of CAL-A (enzyme/substrate ratio, 42 mg) and heptane (2.0 mL).

General procedure for large-scale KR under optimal reaction conditions

rac-**1a** (0.80 mmol, 130 mg) or *rac*-**1b** (0.80 mmol, 105 mg) and vinyl butyrate (10 equiv, 8.0 mmol, 915 mg) were added to a 50-mL two-neck round bottom flask. After complete solubilization of the alcohols, 2:1 m/m of CAL-A (enzyme/substrate ratio, 260 mg for the reaction with *rac*-**1a** or 210 mg for the reaction with *rac*-**1b**) and heptane (10.0 mL) were added to the solution. The resulting suspensions were stirred at 30 °C with a magnetic bar, and the reactions were monitored by GC-FID. After reaching maximum substrate conversions to the (*R*)-products and lower side-product formation, the enzyme was removed with a filter paper and washed with ethyl acetate (2 × 5.0 mL), and the result solutions were concentrated under reduced pressure. The residues were purified by flash chromatography (heptane/ethyl acetate 10:1) to give the isolated enantiomers. This procedure was repeated using vinyl acetate as an acyl donor to provide enantiomer (*R*)-**2a**.

(*S*)-(+)-1-Methyl-1,2,3,4-tetrahydronaphthalen-1-ol ((*S*)-**1a**)

White solid; 66.4 mg (51% yield); 97% *ee*; $[\alpha]_D^{26} +20.8$ (*c* 0.77, CHCl₃, lit.:¹⁴ $[\alpha]_D^{26} +7.2$, *c* 1.0, CHCl₃, 38% *ee*); chiral GC-FID: $t_{R-(S)} = 13.76$ min, $t_{R-(R)} = 15.16$ min (column: CP-Chirasil-DEX CB).

(*S*)-(+)-1-Methyl-2,3-dihydro-1*H*-inden-1-ol ((*S*)-**1b**)

Yellow solid; 50.2 mg (48% yield); 80% *ee*; $[\alpha]_D^{26} +9.7$ (*c* 1.0, CHCl₃, lit.:¹⁴ $[\alpha]_D^{26} +7.9$, *c* 1.0, CHCl₃, 45% *ee*); chiral GC-FID: $t_{R-(S)} = 8.93$ min, $t_{R-(R)} = 9.20$ min (column: CP-Chirasil-DEX CB).

(*R*)-(-)-1-Methyl-1,2,3,4-tetrahydronaphthalen-1-yl acetate ((*R*)-**2a**)

Yellow oil; 10.6 mg (13% yield); > 99% *ee*; $[\alpha]_D^{25} -12.5$ (*c* 0.8, CHCl₃, lit.:¹⁴ $[\alpha]_D^{26} -14.3$, *c* 0.6, CHCl₃, 99% *ee*); chiral GC-FID: $t_{R-(R)} = 10.33$ min, $t_{R-(S)} = 10.86$ min (column: CP-Chirasil-DEX CB).

(*R*)-(-)-1-Methyl-1,2,3,4-tetrahydronaphthalen-1-yl butyrate ((*R*)-**4a**)

Yellow oil; 60.3 mg (37% yield); > 99% *ee*; $[\alpha]_D^{26} -25.2$ (*c* 1.8, CHCl₃); chiral GC-FID: $t_{R-(R)} = 16.14$ min, $t_{R-(S)} = 16.73$ min (column: CP-Chirasil-DEX CB).

(*R*)-1-Methyl-2,3-dihydro-1*H*-inden-1-yl butyrate ((*R*)-**4b**)

Yellow oil; 96% *ee*; chiral GC-FID: $t_{R-(R)} = 11.08$ min, $t_{R-(S)} = 11.22$ min (column: CP-Chirasil-DEX CB). After purification and concentration under reduced pressure, the ester decomposed into unidentified products.

Therefore, it was not possible to determine its optical rotation. The *R* configuration was assigned via chiral GC-FID by comparing the retention times of racemic **4b** with the retention time of chemically esterified (*S*)-**4b** (DMAP-catalyzed esterification of alcohol (*S*)-**1b** 80% *ee*; ester (*S*)-**4b** obtained with 73% *ee*) (see SI for details).

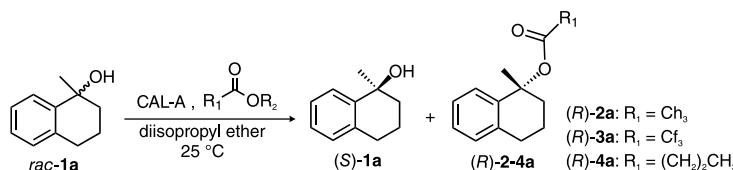
Results and Discussion

Our research group recently published the optimization of the KR of 2-phenyl-3-butyne-2-ol catalyzed by CAL-A.²¹ The optimization was performed using the commercially available propargyl tertiary alcohol and the immobilized wild-type CAL-A and varying the reaction conditions such as temperature, solvent, acyl donor, acyl donor concentration and enzyme loading. Considering that optimizing the reaction conditions is a practical approach for achieving better conversions and enantioselectivity for enzymatic KR protocols, we envisioned that similar improvements could be expanded for the lipase-catalyzed KR of other tertiary alcohols. This work focused on optimizing the reaction conditions of the enzymatic KR of the tertiary alcohols 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (*rac*-**1a**) and 1-methyl-2,3-dihydro-1*H*-inden-1-ol (*rac*-**1b**).

Initially, we evaluated different acyl donors for the KR of *rac*-**1a** via transesterification, starting from the reaction conditions that provided the best result in the literature²⁰ for this substrate (Table 1). Switching from vinyl acetate to other electron-withdrawing and electron-donating substituted acetates led to a decrease in the conversion rate and sometimes resulted in no reaction or activity (Table 1, entries 1-4). However, when vinyl butyrate was used, KR of *rac*-**1a** with 43% conversion and > 99% *ee* for the (*R*)-product in 24 h was observed (Table 1, entry 5), indicating that vinyl esters with an aliphatic chain were more efficient as acyl donors, which was consistent with previous results for lipase-catalyzed KR of secondary alcohols.²⁴⁻²⁶

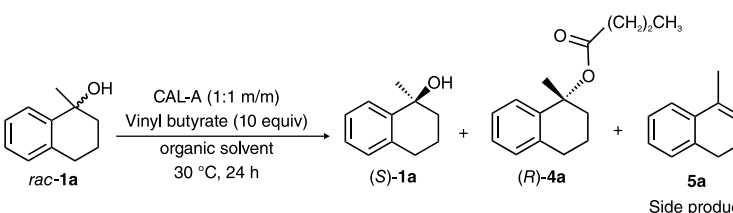
We observed the formation of an alkene (3% yield) as an elimination product in the KR with vinyl butyrate (Table 1, entry 5), as expected due to the reactivity of *rac*-**1a** and stability of tertiary esters like (*R*)-**4a**.^{14,20} Aiming to suppress this side reaction and improve the reaction rate of enzymatic KR, we evaluated other reaction parameters using vinyl butyrate as the acyl donor.

On solvent screening (Table 2), heptane showed results similar to diisopropyl ether, with an increase in alkene formation as a side product (Table 2, entry 2), whereas isooctane led to the maximum conversion of KR and low side product formation (Table 2, entry 3). Compared to diisopropyl ether, these two non-polar solvents are slightly

Table 1. Kinetic resolution (KR) of 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (*rac*-**1a**) using different acyl donors


entry	Acyl donor	Reaction time / h	Product	<i>c</i> ^a / %	<i>ee</i> _{Prod} ^b / %	<i>ee</i> _{Subst} ^b / %	<i>E</i>
1	vinyl acetate	48	(<i>R</i>)- 2a	19	> 99	23	> 200
2	isopropenyl acetate	48	(<i>R</i>)- 2a	8	> 99	9	> 200
3	ethyl acetate	24	(<i>R</i>)- 2a	nr	—	—	—
4	ethyl trifluoroacetate	24	(<i>R</i>)- 3a	nr	—	—	—
5	vinyl butyrate	24	(<i>R</i>)- 4a	43	> 99	> 75	> 200

Conditions: *rac*-**1a** (0.16 mmol, 26 mg), acyl donor (10 equiv, 1.60 mmol), CAL-A (1:1 m/m, 26 mg), diisopropyl ether (2 mL), 30 °C. ^aDetermined by GC-FID analysis with *n*-tetradecane (0.025 mmol mL⁻¹) as internal standard. ^bDetermined by chiral GC-FID analysis. *c*: conversion; *ee*: enantiomeric excess; *E*: enantioselectivity; nr: no reaction observed; CAL-A: lipase A from *Candida antarctica*; GC-FID: gas chromatography-flame ionization detection.

Table 2. Solvent screening of kinetic resolution (KR) of 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (*rac*-**1a**)


entry	Solvent	<i>c</i> ^a / %	<i>ee</i> _{Prod} ^b / %	<i>ee</i> _{Subst} ^b / %	<i>E</i>	Side product / %
1	diisopropyl ether	43	> 99	75	> 200	3
2	heptane	41	> 99	70	> 200	6
3	isooctane	49	97	95	> 200	3
4	acetonitrile	nr	—	—	—	—
5	trifluorotoluene	nr	—	—	—	—

Conditions: *rac*-**1a** (0.16 mmol, 26 mg), vinyl butyrate (10 equiv, 1.60 mmol, 183 mg), CAL-A (1:1 m/m, 26 mg), organic solvents (2 mL), 30 °C, 24 h. ^aDetermined by GC-FID analysis with *n*-tetradecane (0.025 mmol mL⁻¹) as internal standard. ^bDetermined by chiral GC-FID analysis. *c*: conversion; *ee*: enantiomeric excess; *E*: enantioselectivity; nr: no reaction observed; CAL-A: lipase A from *Candida antarctica*; GC-FID: gas chromatography-flame ionization detection.

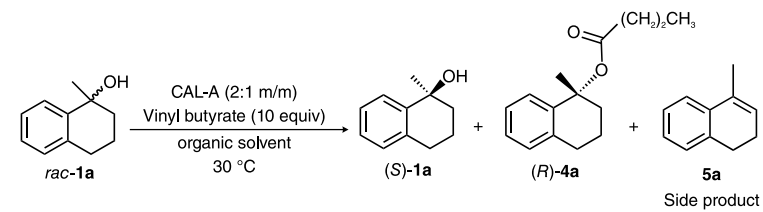
eco-friendly. Polar solvents acetonitrile and trifluorotoluene (Table 2, entries 4 and 5) inhibited enzyme activity. Thus, we selected heptane and isooctane as solvents in the following experiments.

Increasing the enzyme load to an enzyme/substrate ratio of 2:1 m/m increased the speed of the KR by about 5-fold (Table 3), decreasing the reaction time from 24 to 4–5 h and maintaining the exact conversion and selectivities. Increasing the enzyme/substrate ratio to 3:1 m/m did not increase the reaction rates. Therefore, the changes made to the reaction parameters (vinyl butyrate as acyl donor, heptane or isooctane as solvent at 30 °C, and 2:1 m/m enzyme/substrate ratio) led to an optimized enzymatic KR for this challenging substrate.

The optimized protocol was also extended to the KR of the racemic five-membered ring of 1-methyl-2,3-dihydro-

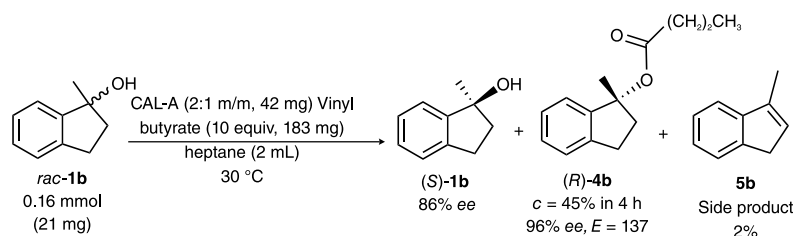
1*H*-inden-1-ol (*rac*-**1b**), affording (*R*)-ester **4b** with 45% conversion and 96% *ee* in only 4 h (Scheme 2). As observed for *rac*-**1a**, this is the best result reported for an enzymatic KR of *rac*-**1b** regarding reaction rate, conversion, and enantioselectivity, highlighting the optimization achieved using vinyl butyrate as the acyl donor.

A large-scale KR of *rac*-**1a–1b** was performed with an increase of 5-fold in substrate loading (0.16 to 0.80 mmol) and using heptane as solvent (Table 4). These experiments demonstrated that the protocol is promising for scaling up and isolating the optically active compounds (*S*)-**1a–1b** and (*R*)-**4a–4b** by column chromatography. We faced difficulty isolating the enantiomers due to the previously mentioned reactivity and stability of the tertiary benzyl bicyclic alcohols and their esters. Using silica as the stationary phase in column chromatography, the esters

Table 3. Increasing enzyme load for kinetic resolution (KR) of 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (*rac*-**1a**)


entry	Solvent	Reaction time / h	<i>c</i> ^a / %	<i>ee</i> _{Prod} ^b / %	<i>ee</i> _{Subst} ^b / %	<i>E</i>	Side product / %
1	heptane	5	43	> 99	75	> 200	3
2	isooctane	4	41	> 99	70	> 200	6

Conditions: *rac*-**1a** (0.16 mmol, 26 mg), vinyl butyrate (10 equiv, 1.60 mmol, 183 mg), CAL-A (2:1 m/m, 52 mg), organic solvents (2 mL), 30 °C. ^aDetermined by GC-FID analysis with *n*-tetradecane (0.025 mmol mL⁻¹) as internal standard. ^bDetermined by chiral GC-FID analysis. *c*: conversion; *ee*: enantiomeric excess; *E*: enantioselectivity; CAL-A: lipase A from *Candida antarctica*; GC-FID: gas chromatography-flame ionization detection.

**Scheme 2.** Kinetic resolution (KR) of 1-methyl-2,3-dihydro-1*H*-inden-1-ol (*rac*-**1b**) under optimal reaction conditions (CAL-A: lipase A from *Candida antarctica*).

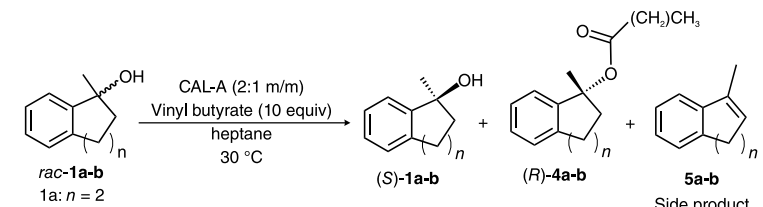
(*R*)-**4a-4b** were easily decomposed into their respective tertiary alcohols and alkenes. Therefore, it was necessary to use neutral alumina to isolate the enantiomers by column chromatography. Even so, it was not possible to isolate the product (*R*)-**4b** (see SI for details).

The optimizations of the KR reaction conditions led to a significant increase in conversion compared to the previous works,^{14,20} reaching almost the maximum of conversion for resolutions of racemates. Also, the conversions of 44–45% (Table 4) were achieved in only 4 or 5 h, which is between 10 and 18 times faster than previously reported.^{14,20} Scheme 3 compares the results obtained in this work

with those previously reported^{14,20} and summarizes the optimizations achieved here.

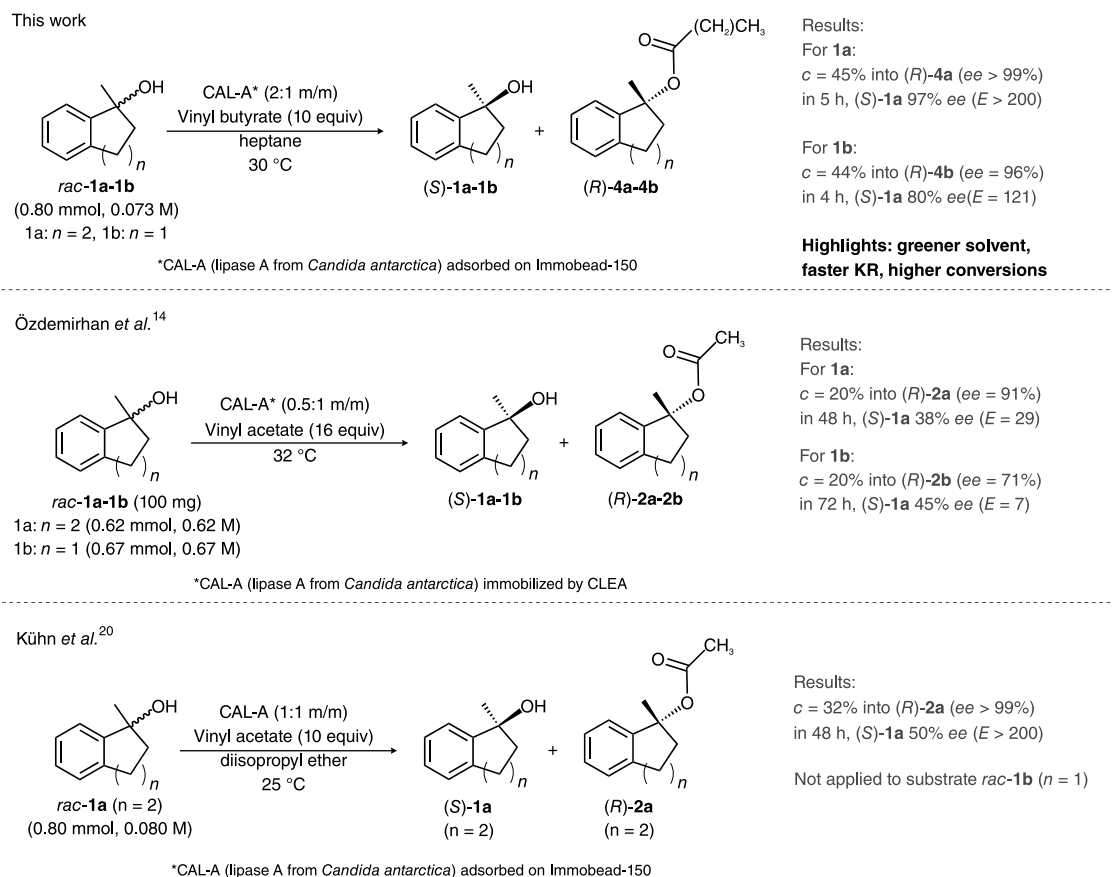
Conclusions

We developed an efficient enzymatic KR method for two tertiary benzyl bicyclic alcohols (*rac*-**1a-1b**) by optimizing the reaction conditions, such as acyl donor, solvent, and amount of a commercially available enzyme. The optimal lipase-catalyzed KR with vinyl butyrate as acyl donor and heptane or isooctane as solvent led to almost the maximum conversion for resolution methods,

Table 4. Large-scale kinetic resolution (KR) of alcohols *rac*-**1a-1b**


entry	Substrate	Reaction time / h	<i>c</i> ^a / %	<i>ee</i> _{Prod} ^b / % ^b	<i>ee</i> _{Subst} ^b / %	<i>E</i>	Side product / %
1	<i>rac</i> - 1a	5	45	> 99	97	> 200	1
2	<i>rac</i> - 1b	4	44	96	80	121	3

Conditions: *rac*-**1a** (0.80 mmol, 130 mg) or *rac*-**1b** (0.80 mmol, 105 mg), vinyl butyrate (10 equiv, 8.0 mmol, 915 mg), CAL-A (2:1 m/m, 260 mg for entry 1 and 210 mg for entry 2), heptane (10 mL), 30 °C. ^aDetermined by GC-FID analysis with *n*-tetradecane (0.025 mmol mL⁻¹) as internal standard. ^bDetermined by chiral GC-FID analysis. *c*: conversion; *ee*: enantiomeric excess; *E*: enantioselectivity; CAL-A: lipase A from *Candida antarctica*; GC-FID: gas chromatography-flame ionization detection.



Scheme 3. Comparison of the enzymatic kinetic resolution (KR) results obtained in this work with literature (references 14 and 20).

providing conversions to the (*R*)-esters of 44–45% and *ee* of 96–99% in only 4 or 5 h. To our knowledge, these are the best results reported for the enzymatic KR of *rac-1a-1b* regarding reaction rate, conversion, and enantioselectivity. The method consists of starting from readily available reagents and biocatalyst and, under the optimized reaction conditions, showed to be a practical approach for the direct obtention of enantiomerically pure tertiary alcohols derived from α -tetralone and α -indanone. We believe that our studies of the reaction conditions will contribute to the search for more direct and cost-effective methods for enantioselective synthesis of sterically hindered tertiary alcohols.

Supplementary Information

Supplementary information containing detailed experimental procedures, spectroscopic and chromatographic data is available free of charge at <http://jbcs.sbq.org.br> as PDF file.

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Author Contributions

Laiza A. de Almeida was responsible for investigation, methodology, formal analysis, writing original draft; Laerte Ganéo Neto for validation, writing-review and editing; Cintia D. F. Milagre for conceptualization, writing-review and editing; Humberto M. S. Milagre for conceptualization, funding acquisition, project administration, writing-review and editing.

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