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Lipase-catalyzed kinetic resolution of β-borylated carboxylic esters

Joel S. Reis, Leandro H. Andrade *

Institute of Chemistry, University of São Paulo, Av. Prof. Lineu Prestes, 748, CEP 05508-900 São Paulo, SP, Brazil

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ABSTRACT

The kinetic resolution of chiral β-borylated carboxylic esters via lipase-catalyzed hydrolysis and transesterification reactions was studied. The enantioselective hydrolysis catalyzed by CAL-B furnished the β-borylated carboxylic acid with reasonable enantiomeric excess (62% ee), while both methyl and ethyl β-borylated carboxylic esters were recovered with excellent ee (>99%). Meanwhile, the transesterification reaction of β-borylated carboxylic esters and several alcohols, catalyzed by CAL-B, only indicated a high selectivity when ethanol and methyl-(β-pinacolylboronate)-butanoate were used as substrates, which gave ethyl-(β-pinacolylboronate)-butanoate with >99% ee.

1. Introduction

Organoboron compounds are widely used in synthetic organic chemistry. Their versatility allows them to be easily converted into many functional groups in addition to their constant use in new carbon–carbon bond forming reactions. Organoboron reagents in cross-coupling reactions have been widely described in the literature due to their high applicability.[1] Both chiral and achiral boron compounds can be prepared by several synthetic methodologies.[2] Focusing our attention on chiral organoboron compounds, especially on those with a boron atom attached directly to the stereogenic center, a literature survey revealed that the main synthetic route to obtain these compounds, besides the Matteson homologation protocol,[2] is a reaction catalyzed by transition metals (i.e., Cu, Ni, Pd) using chiral ligands.[3]

Over the past few years, biocatalysis has been recognized as an important synthetic tool for preparing enantiomerically pure or enriched compounds.[4] The application of enzymes in traditional chemical reactions is an area of growing interest.[5] Despite the importance of chiral boron compounds, enzymatic routes used to make them are rare in the literature. Recently, we have explored the use of enzymes as catalysts of enantioselective reactions involving organoboron compounds, which led to the study of kinetic resolution of boron-containing chiral alcohols and amines mediated by lipases[6] as well as monooxygenases[7] for selective oxidations of organoboron compounds. Herein we report a new approach to prepare chiral β-borylated carboxylic esters via kinetic resolution through hydrolysis and transesterification reactions catalyzed by lipases. This class of organoboron compound can be converted into β-hydroxy esters, β-amino esters, and consequently into their acid derivatives (β-hydroxy acid or β-amino acid), which are attractive building blocks for the synthesis of bioactive compounds.[8] Alternatively, the preparation of β-hydroxy esters can be carried out via the reduction of the corresponding keto esters using isolated oxidoreductases and whole microbial cells.[4a,9] Furthermore, enzymatic deracemization[10] and resolution[11] of racemic β-hydroxy esters have also been employed.

2. Results and discussion

2.1. Synthesis of β-borylated esters (*RS*)-2a–f

The β-borylated esters (*RS*)-**2a–f** were synthesized by the insertion of a Bpin group into a range of α,β-unsaturated carboxylic esters **1a–f**, according to the methodology reported by Yun et al.[3a] These syntheses are shown in Scheme 1.

2.2. Kinetic resolution of (*RS*)-2a–f via hydrolysis reaction

The first approach selected for the kinetic resolution of β-borylated esters was the enantioselective hydrolysis reaction. We carried out enzymatic assays in order to find an appropriate lipase for the enantioselective hydrolysis of compound (*RS*)-**2a**. The efficiency of the enzymatic assays was measured by the ee values of the remaining β-borylated ester (*RS*)-**2a**. Lipases from *Burkholderia cepacia* (BCL), *Pseudomonas cepacia* immobilized on diatomite (PSD-I), *Pseudomonas cepacia* immobilized on ceramic (PSC-II), *Candida antarctica* immobilized on acrylic resin (CAL-B), *Aspergillus niger* (ANL), *Candida rugosa* (CRL), *Candida cylindracea* (CCL), *Mucor miehei* (MML), and *Pseudomonas fluorescens* (PFL) were tested. Among the biocatalysts tested, CAL-B showed the better performance (82% ee for **2a**) while the reactions mediated by PSD-I and PSC-II furnished the ester with low ee (<10%) after 24 h. We

* Corresponding author. Tel.: +55 11 3091 2287.
E-mail address: leandroh@iq.usp.br (L.H. Andrade).

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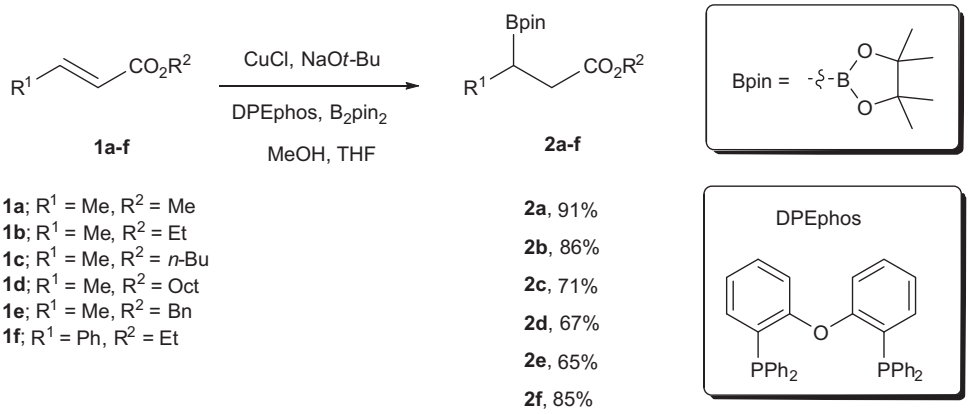
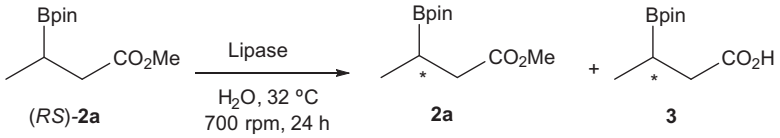


Scheme 1. β-Borylation reaction of esters **1a–f**.

Table 1
Screening of lipases for enantioselective hydrolysis of (*RS*)-**2a**[a]



Entry	Lipase	ee **2a**[b] (%)
1	BCL	No reaction
2	PSD-I	<10
3	PSC-II	<10
4	CAL-B	82[c]
5	ANL	No reaction
6	CRL	No reaction
7	CCL	No reaction
8	MML	No reaction
9	PFL	No reaction

[a] General conditions: H_2O (1 mL), lipase (10 mg), (*RS*)-**2a** (0.05 mmol).
[b] Determined by chiral GC analysis.
[c] ee for **3** = 88%, conversion, $c = 49\%$, enantiomeric ratio, *E*-value = 29. $c = ee_S/(ee_S + ee_P)$; $E = \ln\{[ee_P(1 - ee_S)/(ee_P + ee_S)]\}/\ln\{[ee_P(1 + ee_S)/(ee_P + ee_S)]\}$.[12]

extended the reaction time to 48 h but no increase in the ee value was observed (81% ee for **2a**). The other lipases did not perform the desired hydrolysis (Table 1).

In order to evaluate the effect of organic solvents on the hydrolysis reaction, water-miscible and water-immiscible solvents were employed as well as different ratios between organic solvent/water. Hexane, toluene, *t*-BuOMe, THF, DMF, and dioxane were used as the organic solvents; however, no improvement was detected, yielding low ee values (10–43%) for **2a**. From these results, it was possible to see the clear dependence of a large amount of water to perform efficiently the enzymatic hydrolysis.

We suspected that the β-borylated carboxylic acid **3** could be disturbing the reaction through lipase inactivation; thus, assays under buffered systems were tested. The β-borylated ester **2a** was obtained with reasonable ee (48–71%), however, the values were slightly lower than those obtained with water as the solvent.

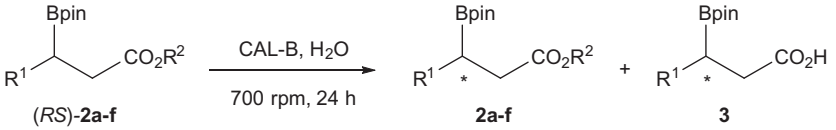
Our protocol was extended to additional compounds (*RS*)-**2b–f**, which present long carbon chains or steric hindrance to the carboxyl group. When ethyl ester (*RS*)-**2b** was submitted to enzymatic hydrolysis conditions a very similar result to that of methyl ester (*RS*)-**2a** was obtained (Table 2, entry 2). Meanwhile, esters with a long carbon chain (*RS*)-**2c–e** caused either a considerable decrease in ee values or no reaction (Table 2, entries 3–5). Ester (*RS*)-**2f**, which contains a phenyl group at the β position, did not undergo the desired hydrolysis (Table 2, entry 6). On the other hand, when we increased the reaction temperature, we obtained excellent ee values (ester **2a** >99% ee, 3 h, Table 2, entry 7). Similarly, compound **2b** was formed in >99% ee in 24 h (Table 2, entry 8). Enzymatic hydrolysis of esters (*RS*)-**2c–f** showed low ee values or no reaction (Table 2, entries 9–13).

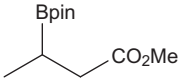
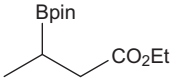
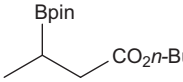
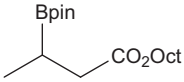
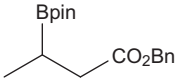
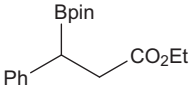
2.3. Determination of the absolute configuration for 2a,b and 3

In order to assign the absolute configuration of **2a**,**b** and **3** and determine the ee of acid **3** produced from the hydrolysis protocol, preparative-scale reactions were carried out (Schemes 2 and 3).

As shown in Scheme 2, the enantioenriched ester **2a** was isolated with 39% yield and >99% ee, while acid **3** was isolated with 49% yield and, after esterification with diazomethane, showed an ee value of 62%. The absolute configuration was assigned after boron oxidation and the values of the specific rotation of the β-hydroxy esters were compared with the literature.[13,14] It is important to note that this oxidation occurs with retention of configuration. The β-hydroxy ester **4a** obtained from ester **2a** has revealed a rotation of +19.2, representing the (*S*)-enantiomer according to the literature.[13] On the other hand, β-hydroxy ester **4a** obtained from acid **3** revealed a rotation of −11.4, representing the (*R*)-enantiomer according to the literature.[14] Similarly, the

Table 2
Enzymatic hydrolysis of β-borylated esters (*RS*)-**2a–f**[a]



Entry	(*RS*)-**2a–f**	T (°C)	ee **2**[b] (%)	ee **3**[c] (%)	*c*[d] (%)	*E*[d]-value
1	 **2a**	32	82	84	49	29
2	 **2b**	32	74	73	50	14
3	 **2c**	32	<10	(–)	(–)	(–)
4	 **2d**	32	No reaction	(–)	(–)	(–)
5	 **2e**	32	No reaction	(–)	(–)	(–)
6	 **2f**	32	No reaction	(–)	(–)	(–)
7[e]	**2a**	70	>99	62	61	29
8	**2b**	70	>99	16	86	7
9	**2c**	70	34	(–)	(–)	(–)
10	**2d**	70	<10	(–)	(–)	(–)
11	**2e**	70	No reaction	(–)	(–)	(–)
12	**2f**	70	No reaction	(–)	(–)	(–)
13[f]	**2f**	70	No reaction	(–)	(–)	(–)

(–) = Not determined due to low or no conversion.
[a] General conditions: H_2O (1 mL), CAL-B (10 mg), (*RS*)-**2a–f** (0.05 mmol).
[b] Analysis after oxidation with $NaBO_3$. For entries 2–5 and 8–11, the ee was measured by chiral GC analysis after acetylation. For entries 6, 12, and 13, the ee was measured by chiral HPLC analysis.
[c] ee was measured by chiral GC analysis after acid derivatization with CH_2N_2.
[d] $c = ee_S/(ee_S + ee_P)$; $E = \ln\{[ee_P(1 - ee_S)/(ee_P + ee_S)]\}/\ln\{[ee_P(1 + ee_S)/(ee_P + ee_S)]\}$.
[e] Reaction time = 3 h.
[f] EtOH (2%) was used as the co-solvent.

enantioenriched ester **2b** was isolated with 41% yield and >99% ee, while acid **3** was isolated with 29% yield and after derivatization, revealed an ee value of 16% (Scheme 3). The specific rotation data show that the (*S*)-enantiomer was recovered, whereas the (*R*)-enantiomer was hydrolyzed. These data lead us to conclude that in the enantioselective enzymatic hydrolysis of esters **2a** or **2b**, CAL-B exhibits an (*R*)-preference. Moreover, considering the size of the groups bonded at stereogenic center, we can conclude that our protocol follows Kazlauskas' rule (Scheme 4).[15]

2.4. Kinetic resolution of (*RS*)-2a–e via transesterification

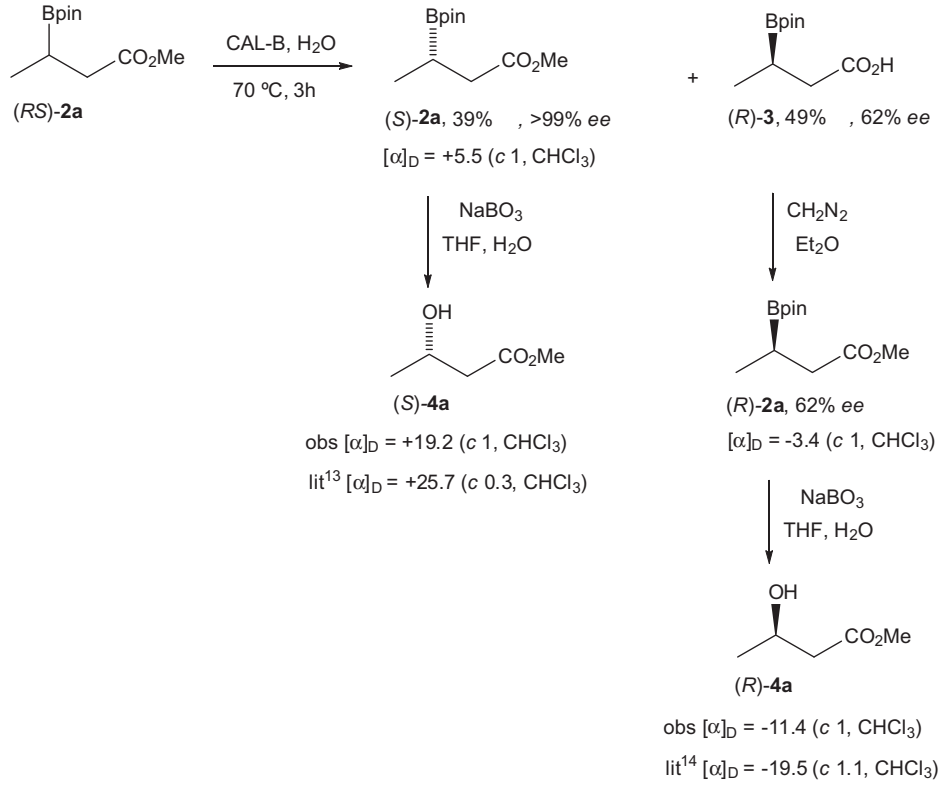
As an alternative to the hydrolysis reaction, we decided to evaluate the enzymatic transesterification reaction to obtain esters **2a–e** in enantiomerically pure form. Different organic solvents, and carbon chains attached to the carboxylic ester and alcohols were employed (Scheme 5). We also carried out some reactions using an additive (Lewis acid) to increase the carboxylic group reactivity (Scheme 6).

Despite the application of several reaction conditions, no transesterification reaction was observed at 32 °C. Thus, we increased the temperature to 70 °C as applied in the hydrolysis reactions and good results were obtained (Scheme 7).

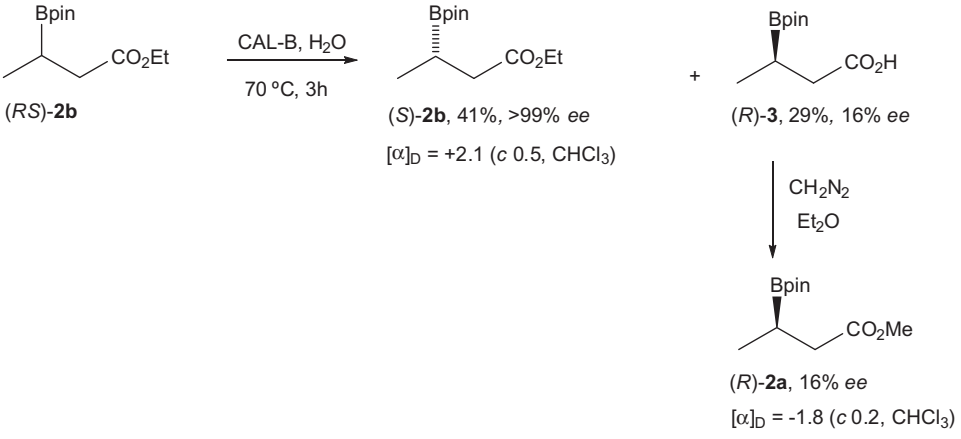
When the methyl ester (*RS*)-**2a** was submitted to the transesterification protocol, we observed that OctOH and BnOH gave no reaction, while *n*-BuOH exhibited a very low conversion (>10%). By changing the alcohol for EtOH, we achieved good results. The produced ethyl ester **2b** (B form) was obtained in enantiomerically pure form using either toluene or hexane as the solvent. For the remaining methyl ester **2a** (A form), reasonable ee values (33% and 44%, respectively) were obtained. Moreover, when employing more concentrated media (0.45 mL of solvent and 0.05 mL of alcohol), similar results were observed. When the reaction was carried out over 48 h, a slight increase in conversion was observed, but with a decrease of ee for the produced ethyl ester **2b** (B form) (96%). By employing only EtOH as the solvent, no reaction was observed. Finally, when esters (*RS*)-**2b–e** were submitted to transesterification reactions, using MeOH or EtOH as the nucleophile, we did not observe the desired products.

3. Conclusion

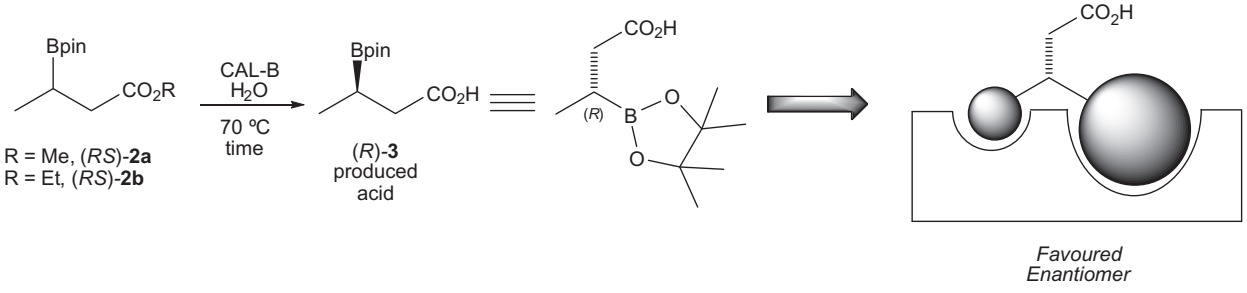
In conclusion, we have shown the lipase-catalyzed resolution of β-borylated carboxylic esters via hydrolysis and transesterification reactions. Enzymatic hydrolysis proved to be a better alternative for obtaining enantiomerically pure boron-containing carboxylic esters than the transesterification reaction. In some cases, the enantioselective enzymatic transesterification provided the produced ester in high enantiomeric excess. However, esters with



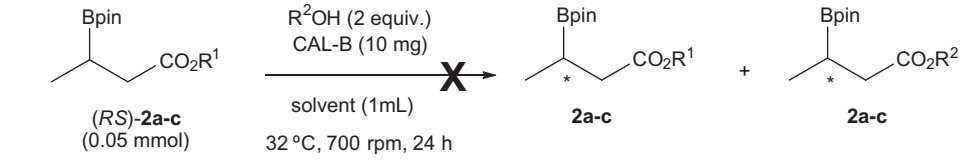
Scheme 2. Transformations of ester (*RS*)-**2a**.



Scheme 3. Transformations of ester (*RS*)-**2b**.

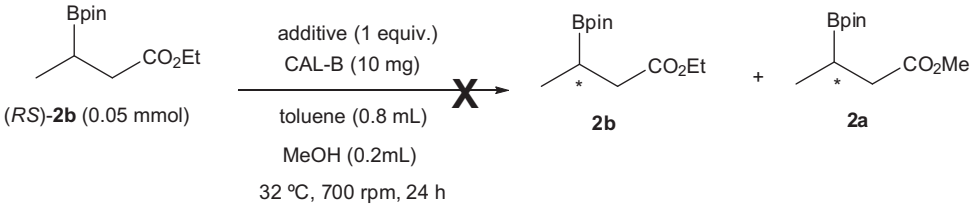


Scheme 4. Kazlauskas' rule for the hydrolysis of ester **2a**,**b**.



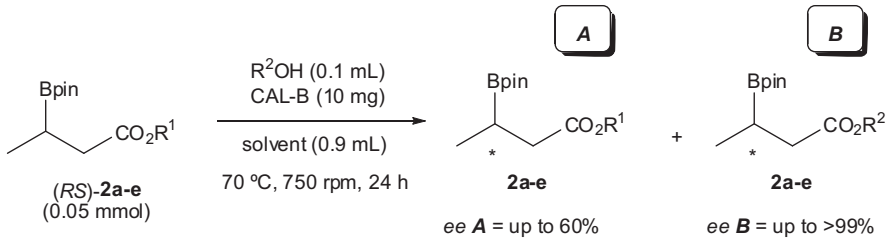
R^1; R^2 = Me, Et, *n*-Bu; solvent = Hexane, Toluene, THF, Dioxane, EtOH, MeOH, *n*-BuOH

Scheme 5. Enzymatic transesterification of (*RS*)-**2a–c**.



additive - $CaCl_2$, $ZnCl_2$, $CoCl_2$, $CuCl_2$, $NiCl_2$, LiCl, $MnCl_2$, $FeCl_3$, $AlCl_3$, $MgCl_2$

Scheme 6. Enzymatic transesterification of (*RS*)-**2b** using an additive.

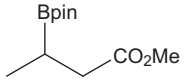
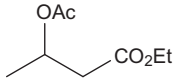
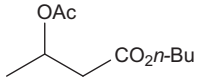
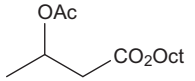
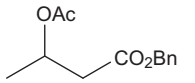
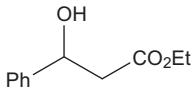


R^1 = Me **2a**, Et **2b**, *n*-Bu **2c**, Oct **2d**, Bn **2e**
R^2OH = BnOH, OctOH, *n*-BuOH, EtOH, MeOH
solvent = toluene, hexane, EtOH

Conv. = up to 32%

Scheme 7. Enzymatic transesterification of (*RS*)-**2a–e** at 70 °C.

Table 3
General conditions for the determination of the enantiomeric excess of the compounds **2a**–**e**

Compound	General conditions
	GC: Column Varian CP-Chirasil-DEX CB β-cyclodextrin (25 m × 0.25 mm × 0.25 μm). Temperature of the detector and injector was 220 °C; H_2 as carrier gas (60 kPa). Oven 80–130 °C, rate 1.5 °C/min. Retention time of enantiomers = (*R*) 19.36 and (*S*) 19.57 min
	GC: Column Varian CP-Chirasil-DEX CB β-cyclodextrin (25 m × 0.25 mm × 0.25 μm). Temperature of the detector and injector was 220 °C; H_2 as carrier gas (80 kPa). Oven 85 (maintenance for 1 min)–110 °C, rate 2.5 °C/min. Plateau of 110 °C (10 min), then heating until 180 °C, rate 10 °C/min. Retention time of enantiomers = (*S*) 5.89 and (*R*) 6.11 min
	GC: Column Varian CP-Chirasil-DEX CB β-cyclodextrin (25 m × 0.25 mm × 0.25 μm). Temperature of the detector and injector was 220 °C; H_2 as carrier gas (80 kPa). Oven 85 (maintenance for 1 min)–110 °C, rate 2.5 °C/min. Plateau of 110 °C (10 min), then heating until 180 °C, rate 10 °C/min. Retention time of enantiomers = 11.96 and 12.36 min
	GC: Column Varian CP-Chirasil-DEX CB β-cyclodextrin (25 m × 0.25 mm × 0.25 μm). Temperature of the detector and injector was 220 °C; H_2 as carrier gas (80 kPa). Oven 85 (maintenance for 1 min)–180 °C, rate 2.5 °C/min. Retention time of enantiomers = 24.87 and 25.32 min
	GC: Column Varian CP-Chirasil-DEX CB β-cyclodextrin (25 m × 0.25 mm × 0.25 μm). Temperature of the detector and injector was 220 °C; H_2 as carrier gas (80 kPa). Oven 85 (maintenance for 1 min)–180 °C, rate 2.5 °C/min. Retention time of enantiomers = 29.03 and 29.33 min
	HPLC: Chiralcel® OB column, hexane/*i*-PrOH (95:5), flow = 1 mL/min, λ = 220 nm. Retention time of enantiomers = 9.99 and 11.57 min

longer carbon chains or steric hindrance at the carboxyl group did not undergo the desired reactions, even at high temperatures.

4. Experimental

4.1. General methods

Unless otherwise noted, commercially available materials were used without further purification. All the enzymes were purchased from the Sigma–Aldrich Chemical Company. All solvents were HPLC or ACS grade. THF was distilled from sodium benzophenone ketyl under nitrogen atmosphere. A note about ^{13}C NMR spectra: due to the boron quadrupole, carbons directly attached to this element are often not detected in ^{13}C NMR spectra.[16] Optical rotations were measured on a Perkin Elmer-343 digital polarimeter in a 1 mL cuvette with a 1 dm path length. All values are reported in the following format: $[\alpha]_D$ = specific rotation (concentration of the solution reported in units of 10 mg sample per 1 mL, solvent used). Gas chromatography (GC) analyses were obtained using a Shimadzu 17-A with chiral column Varian CP-Chirasil-DEX CB β-cyclodextrin (25 m × 0.25 mm × 0.25 μm) and H_2 was used as the carrier gas under an appropriate pressure.

4.2. Synthetic procedures

The α,β-unsaturated esters **1d–e** were synthesized according to the methodology previously established.[17]

4.2.1. (*E*)-Octyl but-2-enoate 1d

^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 6.96 (dq, *J* = 15.6 and 6.8 Hz, 1H), 5.84 (dq, *J* = 15.6 and 1.6 Hz, 1H), 4.03 (m, 2H), 1.88 (dd, *J* = 6.8 Hz and 1.6 Hz, 3H), 1.34–1.20 (m, 8H), 1.05–0.85 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 166.7, 144.2, 122.8, 66.5, 38.7, 30.4, 28.9, 23.8, 22.9, 17.9, 14.0, 10.9. FT-IR (KBr) ν_{max} = 3052, 2960, 1723, 1660, 1265, 1181, 969 cm^{-1}. LRMS (EI) *m*/*z* (%) = 199(1) [M^++1], 183(1), 112(54), 85(21), 84(31), 69(100), 57(41).

4.2.2. (*E*)-Benzyl but-2-enoate 1e

^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.42–7.30 (m, 5H), 7.02 (dq, *J* = 15.6 and 7 Hz, 1H), 5.89 (dq, *J* = 15.6 and 1.8 Hz, 1H), 5.17 (s, 2H), 1.88 (dd, *J* = 7 and 1.8 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 166.2, 145.1, 136.1, 128.4, 128.1, 128.1, 122.4, 65.9, 18.0. FT-IR (KBr) ν_{max} = 3033, 2946, 1721, 1658, 1264, 1174, 1014, 969, 697 cm^{-1}. LRMS (EI) *m*/*z* (%) = 176(10) [M^+], 131(32), 107(13), 91(74), 77(15), 69(100), 51(13), 41(31).

4.2.3. Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-butanoate 2a

For the preparation of β-borylated esters **2a–f** was employed the procedure reported in the literature by Yun et al.[3a] ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 3.65 (s, 3H), 2.45 (dd, *J* = 16.4, 7.8 Hz, 1H), 2.36 (dd, *J* = 16.4, 6.6 Hz, 1H), 1.40–1.30 (m, 1H), 1.24 (s, 12H), 1.00 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 174.2, 83.1, 51.3, 37.4, 24.6, 24.6, 15.0. FT-IR (KBr) ν_{max} = 2978, 1738, 1371, 1320, 1204, 1144, 1012, 859, 670 cm^{-1}. LRMS (EI) *m*/*z* (%) = 228(1) [M^+], 213(21), 170(89), 128(74), 127(64), 112(61), 101(12), 83(84), 59(100), 41(93).

4.2.4. Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-butanoate 2b

^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.12 (q, *J* = 7.2 Hz, 2H), 2.44 (dd, *J* = 16.4, 7.8 Hz, 1H), 2.34 (dd, *J* = 16.4, 6.6 Hz, 1H), 1.42–1.30 (m, 1H), 1.29–1.20 (m, 15H), 1.00 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 173.8, 83.0, 60.1, 37.6, 24.6, 24.6, 15.0, 14.2. FT-IR (KBr) ν_{max} = 2978, 1735, 1370, 1319, 1144, 1032, 857, 670 cm^{-1}. LRMS (EI) *m*/*z* (%) = 242(1) [M^+], 227(12), 184(70), 141(50), 127(12), 113(50), 101(12), 83(100), 59(39), 41(88).

4.2.5. Butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-butanoate 2c

^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.06 (t, *J* = 6.5 Hz, 2H), 2.43 (dd, *J* = 16.4, 7.6 Hz, 1H), 2.34 (dd, *J* = 16.4, 6.8 Hz, 1H), 1.68–1.52 (m, 2H), 1.42–1.28 (m, 3H), 1.24 (s, 12H), 1.00 (d, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 173.9, 83.1, 64.0, 37.6, 30.7, 24.6, 24.6, 19.1, 15.0, 13.6. FT-IR (KBr) ν_{max} = 2961, 1734, 1371, 1319, 1144, 1010, 859, 670 cm^{-1}. LRMS (EI) *m*/*z* (%) = 270(1) [M^+], 255(5), 212(36), 197(22), 155(69), 115(26), 101(27), 83(100), 57(53), 41(97). HRMS (ESI): Calcd for $C_{14}H_{27}BO_4Na$ [M+Na]$^+$ = 293.1900. Found: 293.1893.

4.2.6. Octyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-butanoate 2d

^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 3.95 (m, 2H), 2.45 (dd, *J* = 16.4, 7.6 Hz, 1H), 2.34 (dd, *J* = 16.4, 6.8 Hz, 1H), 1.50–1.25 (m, 10H), 1.24 (s, 12H), 1.00 (d, *J* = 7.4 Hz, 3H), 0.95–0.80 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 174.1, 83.1, 66.5, 38.7, 37.5, 30.3, 28.8, 24.7, 24.6, 23.6, 22.9, 15.0, 14.0, 10.9. FT-IR (KBr) ν_{max} = 2961, 1734, 1464, 1387, 1370, 1319, 1144, 1009, 859, 670 cm^{-1}. LRMS (EI) *m*/*z* (%) = 281(1) [$M^+-3\times Me$], 268(3), 197(15), 155(21), 129(2), 113(23), 101(46), 83(82), 57(90), 41(100). HRMS (ESI): Calcd for $C_{18}H_{35}BO_4Na$ [M+Na]$^+$ = 349.2526. Found: 349.2525.

4.2.7. Benzyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-butanoate 2e

^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.34 (s, 5H), 5.11 (s, 2H), 2.51 (dd, *J* = 16.4, 7.8 Hz, 1H), 2.41 (dd, *J* = 16.4, 6.6 Hz, 1H), 1.50–1.30 (m, 1H), 1.21 (s, 12H), 1.01 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 173.6, 136.1, 128.4, 128.0, 128.0, 83.1, 65.9, 37.6, 24.6, 24.6, 15.0. FT-IR (KBr) ν_{max} = 2977, 1735, 1370, 1319, 1142, 1007, 859, 747, 697 cm^{-1}. LRMS (EI) *m*/*z* (%) = 304(1) [M^+], 289(2), 204(15), 155(29), 113(19), 101(5), 91(100), 83(60), 69(19), 43(45).

4.2.8. Ethyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate 2f

(mp = 51–52 °C, uncorrected). ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.30–7.10 (m, 5H), 4.10 (q, *J* = 7 Hz, 2H), 2.89 (dd, *J* = 13.6, 8.2 Hz, 1H), 2.75 (m, 1H), 2.64 (dd, *J* = 13.4, 5.2 Hz, 1H), 1.22 (t, *J* = 7 Hz, 3H), 1.23–1.16 (m, 12H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 173.3, 141.3, 128.4, 128.1, 125.6, 83.5, 60.3, 37.3, 24.5, 24.4, 14.2. FT-IR (KBr) ν_{max} = 2982, 1730, 1371, 1139, 1022, 848, 770, 707, 535 cm^{-1}. LRMS (EI) *m*/*z* (%) = 304(21) [M^+], 289(1), 233(26), 177(3), 131(33), 117(18), 104(100), 91(10), 83(57), 77(10), 55(19).

4.3. General procedure for oxidation and acetylation of β-borylated esters 2a–f

To a 25 mL round-bottomed flask was added the appropriate β-borylated ester (0.5 mmol), THF (2.5 mL), water (2.5 mL), and $NaBO_3{\cdot}4H_2O$ (2.5 mmol, 0.385 g). The reaction mixture was stirred for 1 h at room temperature and then extracted with ethyl acetate (2 × 5 mL). The organic phase was rinsed with a saturated aqueous solution of NaCl (10 mL) and dried over anhydrous $MgSO_4$. After solvent evaporation, the crude mixture was treated with pyridine (1 mL) and Ac_2O (0.7 mL) and stirred for 12 h at room temperature. The reaction was extracted with ethyl acetate (10 mL) and the organic phase was treated with a saturated aqueous solution of $CuSO_4$ (2 × 10 mL), a saturated aqueous solution of NaCl (2 × 10 mL), and dried over anhydrous $MgSO_4$.

4.4. General procedure for small-scale enzymatic hydrolysis reactions

A 2 mL microtube was charged with the appropriate β-borylated esters (*RS*)-**2a**–**f** (0.05 mmol), CAL-B (10 mg), and ultrapurified water (1 mL, pH 6). The reaction tube was sealed and stirred on a thermomixer (Thermomixer Comfort Eppendorf®) at 700 rpm for appropriate temperatures and times (see Tables 1 and 2). The progress of the reactions was followed by removing samples (30 μL of reaction mixture were added to 600 μL of *t*-BuOMe) for GC or HPLC analysis (Section 4.7).

4.5. General procedure for preparative-scale enzymatic reactions

A 100 mL Schlenk tube was charged with the appropriate β-borylated ester (*RS*)-**2a** or (*RS*)-**2b** (1 mmol), CAL-B (200 mg), and ultrapurified water (20 mL, pH 6). The tube was sealed and the reaction was stirred (magnetic stirrer) in an oil bath at 75 °C (oil temperature) until the appropriate time. Next, the enzyme was decanted, washed with *t*-BuOMe (2 × 10 mL) and the water was extracted with *t*-BuOMe (2 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and after evaporation, the crude mixture was purified by column chromatography on silicagel, using hexanes/EtOAc (8:2) and then EtOAc as eluent.

4.6. General procedure for small-scale enzymatic transesterification reactions

A 10 mL glass tube was charged with the β-borylated esters (*RS*)-**2a** (11.5 mg, 0.05 mmol), CAL-B (10 mg), hexane (0.9 mL), and EtOH (0.1 mL). The reaction tube was sealed and stirred on a thermomixer (Thermomixer Comfort Eppendorf®) at 750 rpm, at 70 °C for 24 h. The progress of the reactions was followed by removing samples (30 μL of reaction mixture were added to 600 μL of *t*-BuOMe), with derivatization as described in Section 4.3, and then analyzed by GC or HPLC (Section 4.7).

4.7. Determination of the enantiomeric excess (ee)

The enantiomeric excesses of the β-borylated esters and their derivatives were measured by chiral HPLC or GC analysis (Table 3). However in some cases, derivatization reactions were carried out as described in Table 2 and Section 4.3.

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