Tetrahedron: *Asymmetry* 22 (2011) 1772–1777

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# Stereocomplementary asymmetric bioreduction of boron-containing ketones mediated by alcohol dehydrogenases

Thiago Barcellos [a], Katharina Tauber [b], Wolfgang Kroutil [b,*], Leandro H. Andrade [a,*]

[a] *Institute of Chemistry, University of São Paulo, Av. Prof. Lineu Prestes 748, CEP 05508-900 São Paulo, SP, Brazil*
[b] *Department of Chemistry, Organic and Bioorganic Chemistry, University of Graz, Heinrichstrasse 28, A-8010 Graz, Austria*

ARTICLE INFO

*Article history:*
Received 20 September 2011
Accepted 26 October 2011

ABSTRACT

Optically active boron-containing alcohols were prepared via the stereoselective reduction of the corresponding carbonyl compounds by alcohol dehydrogenases. Depending on the substrate, both (*R*)-alcohols and (*S*)-alcohols were obtained with excellent enantioselectivity (up to >99% ee) employing either ADH-A or LB-ADH.



## 1. Introduction

Boron-containing organic compounds have received considerable attention due to their importance as synthetic intermediates in organic synthesis.[1] Boronic acids and their derivatives are employed in a broad range of organic reactions, mainly as nucleophilic partners in cross-coupling reactions with organic electrophiles, leading to the formation of new carbon–carbon bonds.[2,3]

In addition to their synthetic applications, organoboron compounds have shown significant biological properties,[4] primarily due to the known inhibitory effect against the 20S proteasome.[5] Furthermore, boronic acids and their esters have shown inhibitory activity against other classes of enzyme, such as lipases[6] and glycosyltransferases.[7]

Although new synthetic routes to obtain chiral and achiral boron-containing compounds have been intensely investigated,[8] very few reports regarding the use of enzymatic methodologies in boron chemistry have been described.[9,10] As part of our current interest in biocatalytic reactions applied to boron chemistry, we herein report the first study involving the bioreduction of boron-containing carbonyl compounds mediated by enantiocomplementary alcohol dehydrogenases (ADHs).

The stereoselective reduction of carbonyl compounds by alcohol dehydrogenases and their cofactors has numerous advantages compared to classical chemical reactions and has gained increased relevance over the past few years, in particular for the synthesis of important intermediates for pharmaceuticals and bioactive compounds.[11]

For instance, the alcohol dehydrogenase ADH-A isolated from the bacterium *Rhodococcus ruber* DSM 44541 possesses a high tolerance towards co-solvents, primarily acetone and 2-propanol, and accepts a broad range of ketones.[12] 2-Propanol acts as a hydrogen donor that enables the in situ recycling of the requisite nicotinamide cofactor NADH; in addition 2-propanol helps to solubilise more hydrophobic ketone substrates. Recently, the structure of this enzyme has been published.[13] ADH-A preferentially reduces small-bulky ketones to the (*S*)-alcohol, while the alcohol dehydrogenase from *Lactobacillus brevis* (LB-ADH)[14] produces the (*R*)-enantiomer; thus the two enzymes are stereocomplementary.

## 2. Results and discussion

A series of boron-containing ketones (**1a**–**i**, Fig. 1) were employed as substrates for the bioreduction. We explored the effect of different moieties attached at the ketone and the nature of the boron species. Thus, aromatic, allylic, aliphatic ketones containing pinacol boronate ester or boronic acid group were selected as substrates.

Three different ADHs were chosen for this study; ADH-A, LB-ADH, an ADH from a *Ralstonia* sp., whereby LB-ADH is enantiocomplementary to the two other ADHs (Scheme 1, Table 1).

When the ADH from *Ralstonia* sp. was employed, only ketone **1a** could be reduced, leading to the corresponding alcohols (*S*)-**2a** with only 5% conversion, although alcohol (*S*)-**2a** was obtained with excellent enantiomeric excess (ee >99%). Employing the ADHs from *R. ruber* and *L. brevis* excellent conversions and enantioselectivies were obtained; thus alcohols (*S*)-**2a** and (*R*)-**2a** were obtained with excellent enantiomeric purity (ee >99%) (Table 1, entries 1–3). ADH-A led to the (*S*)-enantiomer while LB-ADH gave access to the (*R*)-enantiomer. The conversions were >99% for ADH-A and 47% for LB-ADH, that is LB-ADH showed a lower activity. Furthermore, bioreductions in the presence of a co-solvent (diethyl ether) did not lead to an improvement of conversion; in

* Corresponding authors. Tel.: +55 1130912287; fax: +55 1138155579 (L.H.A.).
*E-mail addresses:* wolfgang.kroutil@uni-graz.at (W. Kroutil), leandroh@iq.usp.br (L.H. Andrade).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.10.012

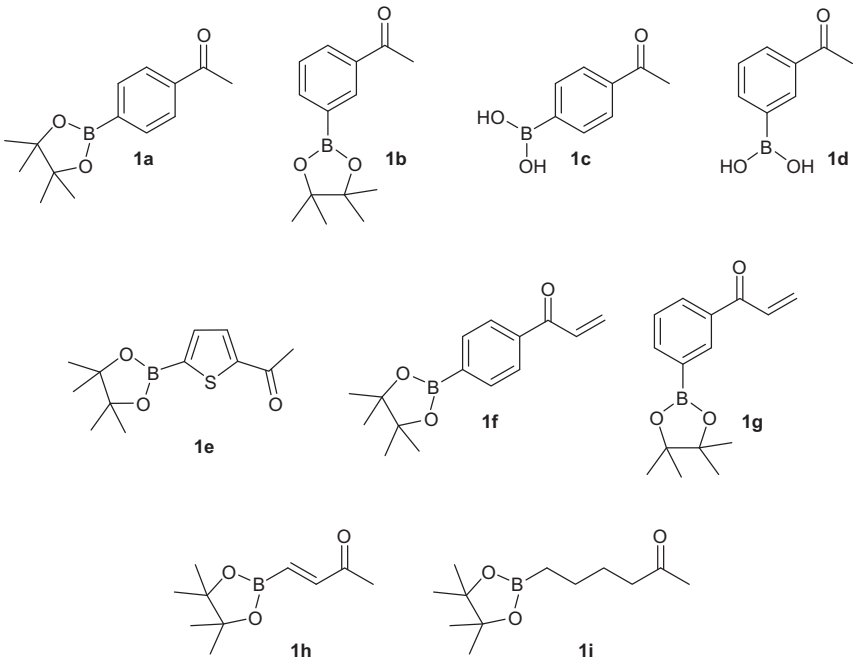
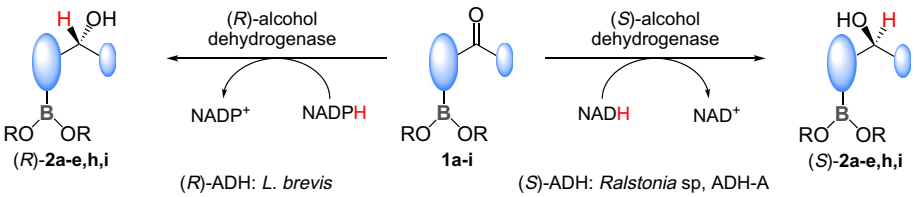



**Figure 1.** Boron-containing ketones.




**Scheme 1.** Bioreduction of boron-containing ketones by ADH.

the case of LB-ADH diminished stereoselectivity was observed for ketone **1a** and LB-ADH (entry 4). In contrast, for ADH-A the co-solvent did not diminish its excellent stereoselectivity.

Both enzymes ADH-A and LB-ADH accepted nicely most of the boron derivatives investigated affording the desired alcohols with excellent enantioselectivity as shown in Table 1.

ADH-A catalysed the reduction of ketone **1b** (entries 5 and 6), bearing boronic ester group at the *meta*-position, with a decrease in conversion compared to the reduction of **1a** under the same reaction conditions; thus alcohol (*S*)-**2b** was obtained with an 87% conversion. However, the reduction of **1b** dropped significantly when LB-ADH was used as the biocatalyst, giving alcohol (*R*)-**2b** at only 3% conversion (entries 7 and 8).

ADH-A was able to efficiently reduce ketones **1c** and **1d** bearing boronic acid groups at the *para*- as well as the *meta*-positions (entries 9, 10, 13 and 14). In contrast, LB-ADH did only accept the ketone **1c** with a boronic acid at the *para*-position (entries 11 and 12), but the conversion dropped significantly in the case where the boronic acid moiety was at the *meta*-position (**1d**, entries 15 and 16).

When ketone **1e** was used as the substrate with ADH-A as the biocatalyst (entries 17 and 18), alcohol **2e** was obtained with a 50% conversion.

However, α,β-unsaturated ketones **1f**–**g** (entries 21–28) bearing the terminal C=C bond were not suitable as substrates for the bioreduction with the ADHs evaluated. Neither the desired product nor any side-product was observed. However, the α,β-unsaturated ketone **1h**, which contained an internal double bond, was well accepted by ADH-A, leading to the allylic alcohol (*S*)-**2h** with excellent conversion (>99%) and ee (>99%) (entries 29 and 30).

Additionally, the aliphatic ketone **1i** (entries 33 and 34), containing a boronic ester group at the ω-position was well accepted by ADH-A, leading to alcohol (*S*)-**2i** with high conversion (92%) and enantiomeric excess (>99%). LB-ADH gave alcohol (*R*)-**2i** with a 14% conversion and excellent stereoselectivity (>99% ee).

Comparing these results with previous studies,[12] it can be anticipated that the presence of the boron moiety in the aromatic ketones does not influence the reactivity of these substrates with ADH.

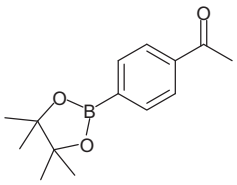
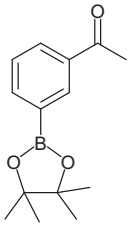
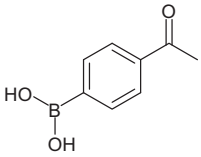
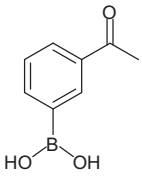
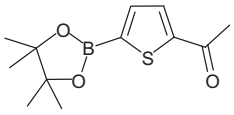
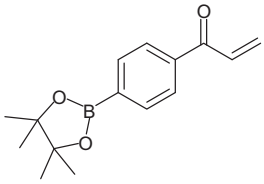
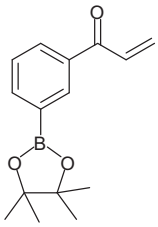
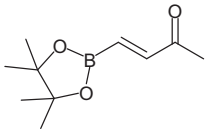
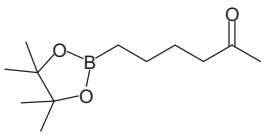
## 3. Conclusion

In conclusion, we have shown herein that optically active boron-containing chiral alcohols can be successfully prepared by the stereoselective reduction of carbonyl compounds by alcohol dehydrogenases. Almost all of the ketones were reduced to the corresponding alcohols with high conversions and excellent enantiomeric excess (up to 99%) especially when ADH from *R. ruber* (ADH-A) was employed.

ADH-A and LB-ADH transformed substrates bearing a boronic ester or a boronic acid moiety at the *para*-position with comparable conversions. ADH-A also accepted a boronic ester or a boronic acid moiety at the *meta*-position.

To the best of our knowledge, this is the first time that boron-containing compounds have been employed as substrates in alcohol dehydrogenase-catalysed reactions

**Table 1**
Bioreduction of boron-containing ketones catalysed by alcohol dehydrogenases from *Rhodococcus ruber* (ADH-A) and *Lactobacillus brevis* (LB-ADH)[a]

| Entry | Substrate | ADH | Alcohol | |
|---|---|---|---|---|
| | | | Conversion[c] (%) | Enantiomeric excess[d] (%) |
| 1 | **1a**  | ADH-A | >99 | >99 (*S*) |
| 2 | | ADH-A[b] | >99 | >99 (*S*) |
| 3 | | LB-ADH | 47 | >99 (*R*) |
| 4 | | LB-ADH[b] | 30 | 94 (*R*) |
| 5 | **1b**  | ADH-A | 87 | >99 (*S*) |
| 6 | | ADH-A[b] | 86 | >99 (*S*) |
| 7 | | LB-ADH | 3 | 99 (*R*) |
| 8 | | LB-ADH[b] | 3 | 99 (*R*) |
| 9 | **1c**  | ADH-A | 91 | >99 (*S*) |
| 10 | | ADH-A[b] | 91 | >99 (*S*) |
| 11 | | LB-ADH | 44 | >99 (*R*) |
| 12 | | LB-ADH[b] | 43 | >99 (*R*) |
| 13 | **1d**  | ADH-A | 84 | >99 (*S*) |
| 14 | | ADH-A[b] | 83 | >99 (*S*) |
| 15 | | LB-ADH | <2 | — |
| 16 | | LB-ADH[b] | <2 | — |
| 17 | **1e**  | ADH-A | 50 | 96 (*S*) |
| 18 | | ADH-A[b] | 50 | 95 (*S*) |
| 19 | | LB-ADH | 4 | 67 (*R*) |
| 20 | | LB-ADH[b] | <2 | 79 (*R*) |
| 21 | **1f**  | ADH-A | n.c. | — |
| 22 | | ADH-A[b] | n.c. | — |
| 23 | | LB-ADH | n.c. | — |
| 24 | | LB-ADH[b] | n.c. | — |
| 25 | **1g**  | ADH-A | n.c. | — |
| 26 | | ADH-A[b] | n.c. | — |
| 27 | | LB-ADH | n.c. | — |
| 28 | | LB-ADH[b] | n.c. | — |
| 29 | **1h**  | ADH-A | >99 | >99 (*S*) |
| 30 | | ADH-A[b] | >99 | >99 (*S*) |
| 31 | | LB-ADH | n.c. | — |
| 32 | | LB-ADH[b] | n.c. | — |
| 33 | **1i**  | ADH-A | 92[e] | >99 (*S*)[e] |
| 34 | | LB-ADH | 14[e] | >99 (*R*)[e] |

[a] Reaction conditions: substrate (50 mM), 2-PrOH (100 μM), phosphate buffer (50 mM, pH 7.5), NADH (1 mM in case of ADH-A), NADPH (1 mM in case of LB-ADH), ADH (150 μL, thermic precipitated), LB-ADH (300 μL, crude extract), 24 h, 30 °C, 120 rpm.
[b] Diethyl ether was employed as a co-solvent (20 μL).

[c] Determined by GC analysis.
[d] Determined by chiral HPLC analysis.
[e] Conversion and ee were determined for the corresponding acetate derivative by CG analysis, (—) = not determined duo to low or none conversion. n.c. = no conversion.

## 4. Experimental

### 4.1. General

Unless otherwise noted, commercially available materials were used without further purification. The boron-containing ketones **1c**, **1d** are commercially available from Sigma-Aldrich. Ketones **1a**, **1b** and the alcohols **2a**, **2b**, **2h** and **2i** were synthesized as previously described.[10a]

All solvents were of HPLC or ACS grade. Solvents used for moisture sensitive operations were distilled from drying reagents under a nitrogen atmosphere: THF was distilled from Na/benzophenone. $CH_2Cl_2$ was distilled from $CaH_2$.

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini 200 spectrometer at operating frequencies of 200 MHz ($^1$H NMR) or 50 ($^{13}$C NMR). The $^1$H NMR chemical shifts are reported in ppm relative to the TMS peak. Data are reported as follows: chemical shift ($\delta$), multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet) and coupling constant ($J$) in Hertz and integrated intensity. The $^{13}$C NMR chemical shifts are reported in ppm relative to $CDCl_3$ or DMSO-$d_6$ signal. The $^{11}$B NMR spectra were obtained on a Varian Inova 300 spectrometer equipped with the appropriate decoupling accessories. All $^{11}$B chemical shifts were referenced to external $BF_3{\cdot}OEt_2$ (0.00 ppm). A note about the $^{13}$C NMR spectra: due to the boron quadrupole, carbons directly attached to this element are often not detected in the $^{13}$C spectra.[15]

Low-resolution mass spectra were obtained on a GC/MS Shimadzu spectrometer, operating at 70 eV. High-resolution mass spectra (HRMS) were acquired using a Bruker Daltonics MicroTOF instrument, operating in an electrospray ionization (ESI) mode.

Gas chromatography (GC) analyses for the measurement of enantiomeric excesses were obtained using a Shimadzu 17-A Gas Chromatograph, equipped with autosampler, Flame Ionization Detector (FID) and a chiral column Varian CP-Chirasil-DEX CB β-cyclodextrin (25 m × 0.25 mm × 0.25 μm). The temperature of the detector and injector was 220 °C; flow = 100 kPa, $H_2$.

High performance liquid chromatograph (HPLC) analyses for the measurement of enantiomeric excesses were performed on a Shimadzu, LC-10AD liquid chromatograph equipped with autosampler and a variable wavelength UV detector (deuterium lamp 190–600 nm). Chiral columns: Chiralcel® OJ-H (0.46 cmφ × 25 cm) or Chiralcel® OD (0.46 cmφ × 25 cm) from Daicel Chemical Ind. *i*-PrOH and hexanes (60% *n*-hexane) HPLC grade purchased from J. T. Baker were used as the eluting solvents.

The alcohol dehydrogenase ADH-A was used as a heat treated crude recombinant enzyme preparation and prepared as previously described.[13] The alcohol dehydrogenase from *L. brevis* was used as a crude enzyme extract from the wild type strain *L. brevis* DSM 20054. The strain was grown in an MRS-Medium (casein peptone 10 g/L, peptone bact. 10 g/L, yeast extract 5 g/L, glucose 20 g/L, Tween 80 1 g/L, potassium hydrogen phosphate 2 g/L, sodium acetate tetrahydrate 8.3 g/L, ammonium citrate 2 g/L, magnesium sulphate heptahydrate 0.2 g/L, manganese chloride tetrahydrate 0.058 g/L) under 'anaerobic conditions', thus without shaking, at 30 °C for three days. Cells were harvested and disrupted using ultrasonification (1 s pulse, 2 s pause, 20 min, 40° intensity), followed by centrifugation (30 min 18,000 rpm, 4 °C). The supernatant containing the LB-ADH was then stored at −20 °C.

### 4.2. Synthesis of 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)ethanone 1e

The (5-acetylthiophen-2-yl)boronic acid (5 mmol, 850 mg) and pinacol (5 mmol, 591 mg) were added to a 50 mL, two-necked, round-bottomed flask containing anhydrous THF (30 mL). The resulting solution was evaporated under reduced pressure at 40 °C. This procedure was repeated (3 times) until TLC analysis indicated complete conversion. The crude product was purified by column chromatography using hexanes/EtOAc (8:2) as the eluent. Compound **1e** was obtained as a white solid (mp = 67.9–68.8 °C). Yield: 1.221 g (97%). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 1.35 (s, 12H), 2.58 (s, 3H), 7.58 (d, $J$ = 3.8 Hz, 1H), 7.73 (d, $J$ = 3.8 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 24.86, 27.56, 84.77, 132.81, 137.39, 149.62, 190.71. $^{11}$B NMR (96 MHz, $CDCl_3$) $\delta$ = 28.90. HRMS [ESI (+)]: Calculated for $C_{12}H_{17}BO_3SNa$ $[M+Na]^+$ = 275.0889; found: 275.0885.

### 4.3. Synthesis of 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)ethanol 2e

Compound **1e** (3 mmol, 756 mg) was added to a 50 mL, two-necked, round-bottomed flask containing anhydrous methanol (10 mL). The resulting solution was cooled to 0 °C with an ice bath. Next, $NaBH_4$ (3.6 mmol, 136 mg) was added, and the mixture was stirred for 0.5 h at 0 °C and for an additional 3.5 h at room temperature. The mixture was cooled to 0 °C and treated with 1 N HCl aqueous solution until pH 7. The mixture was then extracted with EtOAc (3 × 5 mL), dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using hexanes/EtOAc (8:2) as eluent. Compound **2e** was obtained as a colourless oil. Yield: 671 mg (88%). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 1.33 (s, 12H), 1.59 (d, $J$ = 6.6 Hz, 3H), 5.15 (m, 1H), 7.05 (dd, $J$ = 3.6, 0.8 Hz, 1H), 7.50 (d, $J$ = 3.6 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 24.92, 25.59, 66.43, 84.27, 124.82, 137.36, 157.58. $^{11}$B NMR (96 MHz, $CDCl_3$) $\delta$ = 29.00. HRMS (ESI): Calculated for $C_{12}H_{19}BO_3SNa$ $[M+Na]^+$ = 277.1046; found: 277.1042.

### 4.4. Synthesis of 1-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)prop-2-en-1-ol (*RS*)-2f,g

The corresponding 1-(bromophenyl)prop-2-en-1-ol (115 mg, 5 mmol) was added to a 100 mL, two-necked, round-bottomed flask containing anhydrous THF (20 mL). The resulting solution was cooled to −70 °C and *n*-BuLi (10 mmol) was added dropwise via syringe. After the reaction mixture was stirred for 30 min at −70 °C, B(O*i*-Pr)$_3$ (1.880 g, 10 mmol) was added dropwise. The reaction mixture was stirred for 1 h at −70 °C, and then the cooling bath was removed. An aqueous HCl solution (1 mol L$^{-1}$, 10 mL) was added dropwise at 0 °C, and the reaction mixture was stirred for 10 min. The organic phase was removed and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organics were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting solid was solubilized with THF (20 mL) and pinacol was added (5 mmol). The resultant solution was evaporated under reduced pressure at 40 °C. This procedure was repeated (3 times) until TLC analysis indicated complete conversion. The crude product was purified by column chromatography using hexanes/EtOAc (4:1) as the eluent.

#### 4.4.1. 1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl)prop-2-en-1-ol (*RS*)-2f

Obtained as a colourless oil. Yield: 923 mg (71%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.34 (s, 12H), 1.99 (br, 1H), 5.15–5.35 (m, 3H), 6.03 (ddd, $J$ = 17.1, 10.2, 6 Hz, 1H), 7.38 (d, $J$ = 7.8 Hz, 2H), 7.80 (d, $J$ = 7.8 Hz, 2H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 25.05, 75.49, 84.01, 115.8, 125.78, 135.25, 140.31, 145.92. $^{11}$B NMR (96 MHz, $CDCl_3$) $\delta$ = 30.12. HRMS (ESI): Calculated for $C_{15}H_{21}BO_3Na$ $[M+Na]^+$: 283.1262, found: 283.1265.

#### 4.4.2. 1-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl)prop-2-en-1-ol (*RS*)-2g

Obtained as a colourless oil. Yield: 897 mg (69%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.34 (s, 12H), 2.14 (br, 1H), 5.15–5.40 (m, 3H), 6.06 (ddd, $J$ = 17.0, 10.2, 6 Hz, 1H), 7.37 (t, $J$ = 7.7 Hz, 1H), 7.49 (dt, $J$ = 7.7, 1.7 Hz, 1H), 7.74 (dt, $J$ = 7.7, 1.3 Hz, 1H), 7.79 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 25.03, 75.48, 84.02, 115.17, 128.17, 129.46, 132.85, 134.38, 140.49, 142.21. $^{11}$B NMR (96 MHz, $CDCl_3$) $\delta$ = 30.14. HRMS (ESI): Calculated for $C_{15}H_{21}BO_3Na$ $[M+Na]^+$: 283.1262, found: 283.1263.

### 4.5. General procedure for the preparation of ketones 1f–i

The appropriate alcohol (2 mmol) was added to a 50 mL, two-necked, round-bottomed flask containing anhydrous dichloromethane (10 mL). The mixture was cooled to 0 °C and pyridinium dichromate (3 mmol, 1.128 g) was then added. The reaction was monitored by TLC until consumption of the starting material.

Diethyl ether (10 mL) was added, and the precipitate formed was decanted and washed with diethyl ether (3 × 10 mL). The solvent was filtered through a column of Celite. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using hexanes/EtOAc (8:2) as eluent.

#### 4.5.1. 1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl)prop-2-en-1-one 1f

Obtained as a yellow oil. Yield 232 mg (45%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.36 (s, 12H), 5.94 (dd, $J$ = 10.6, 1.7 Hz, 1H), 6.43 (dd, $J$ = 17.2, 1.7 Hz, 1H), 7.15 (dd, $J$ = 17.2, 10.6 Hz, 1H), 7.91 (s, 4H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 25.11, 84.44, 127.89, 130.48, 132.81, 135.15, 139.52, 192.79. $^{11}$B NMR (96 MHz, $CDCl_3$) $\delta$ = 30.14. HRMS (ESI): Calculated for $C_{15}H_{19}BO_3Na$ $[M+Na]^+$: 281.1325, found: 281.1367.

#### 4.5.2. 1-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl)prop-2-en-1-one 1g

Obtained as a yellow oil. Yield 243 mg (47%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.36 (s, 12H), 5.92 (dd, $J$ = 10.5, 1.8 Hz, 1H), 6.44 (dd, $J$ = 17.1, 1.8 Hz, 1H), 7.23 (dd, $J$ = 17.1, 10.5 Hz, 1H), 7.48 (t, $J$ = 7.8 Hz, 1H), 7.95–8.13 (m, 2H), 8.36 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 25.07, 84.33, 128.28, 130.15, 131.50, 132.72, 135.13, 136.92, 139.43, 191.23. $^{11}$B NMR (96 MHz, $CDCl_3$) $\delta$ = 30.17 HRMS (ESI): Calculated for $C_{15}H_{19}BO_3Na$ $[M+Na]^+$: 281.1325, found: 281.1368.

#### 4.5.3. (*E*)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-2-one 1h

Obtained as a colourless oil. Yield: 149 mg (38%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.30 (s, 12H), 2.30 (s, 3H), 6.54 (d, $J$ = 18.6 Hz, 1H), 6.81 (d, $J$ = 18.6 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 28.87, 26.78, 84.25, 146.60, 199.04. $^{11}$B NMR (96 MHz, $CDCl_3$) $\delta$ = 30.00. HRMS (ESI): Calculated for $C_{10}H_{17}BO_3Na$ $[M+Na]^+$ = 219.1168; found: 219.1165.

#### 4.5.4. 6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-one 1i

Obtained as a colourless oil. Yield: 90 mg (20%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 0.78 (t, $J$ = 7.0 Hz, 2H), 1.24 (s, 12H), 1.32–1.62 (m, 4H), 2.12 (s, 3H), 2.41 (t, $J$ = 7.0 Hz, 2H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 23.90, 25.07, 26.75, 30.03, 43.95, 83.23, 209.57. $^{11}$B NMR (96 MHz, $CDCl_3$) $\delta$ = 34.15. HRMS (ESI): Calculated for $C_{12}H_{23}BO_3Na$ $[M+Na]^+$ = 249.1638; found: 249.1636.

### 4.6. General procedure for the bioreduction of boron-containing ketones 1a–i catalysed by ADH-A and ADH-LB

To a phosphate buffer solution (50 mM, pH 7.5, 1 mM NADPH in the case of ADH-LB or 1 mM NADH in the case of ADH-A), substrates (50 mM), 2-propanol (100 μL) and ADH-A (150 μL, thermic precipitated) or ADH-LB (300 μL, crude extract) were added leading to a final volume of 1 mL. Samples were incubated for 24 h at 30 °C and 120 rpm.

The reaction was stopped by the addition of diethyl ether (500 μL). The mixture was mixed thoroughly and centrifuged for 5 min at 13,000 rpm. Then the organic layer was separated from the aqueous phase and the procedure was repeated with diethyl ether (400 μL). The combined organic layers were dried ($Na_2SO_4$) and the supernatant was transferred into GC-glass-vials for analysis.

### 4.7. General procedure for the bioreduction of boron-containing ketone 1a catalysed by ADH-A

Ketone **1a** (100 mg) was used in a 10 mL reaction volume (6 mL phosphate buffer, 50 mM, pH 7.5; 5.3 mg NADH; 1.2 mL ADH-A, thermic precipitated; 800 μL 2-propanol).

The reaction was stopped by extraction with diethyl ether (5 mL) and centrifuged for 5 min at 13,000 rpm. Then the organic layer was separated from the aqueous phase and the procedure was repeated with diethyl ether (5 mL). The combined organic layer was dried ($Na_2SO_4$) prior to analysis (alcohol **2a**, 80% yield).

## Acknowledgments

We thank FAPESP (São Paulo Research Foundation) and CNPq (National Council for Scientific and Technological Development) for financial support.

## References

1. Hall, D. G. *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, Germany, 2005.
2. For reviews concerning the Suzuki-Miyaura reaction, see: (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473; (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419–2440; (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695; (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
3. Potassium organotrifluoroborates in palladium-catalyzed crosscoupling reactions: (a) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240–9261; (b) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288–325; (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286; (d) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49–56; (e) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658.
4. (a) Touchet, S.; Carreaux, F.; Carboni, B.; Bouillon, A.; Boucher, J. *Chem. Soc. Rev.* **2011**, *40*, 3895–3914; (b) Dembitsky, V. M.; Al Quntar, A. A.; Srebnik, M. *Chem. Ver.* **2011**, *111*, 209–237; (c) Trippier, P. C.; McGuigan, C. *Med. Chem. Commun.* **2010**, *1*, 183–198; (d) Nakamura, H.; Watanabe, M.; Ban, H. S.; Nabeyama, W.; Asai, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3220–3224; (e) Borissenko, L.; Groll, M. *Chem. Rev.* **2007**, *107*, 687–717.
5. (a) Dorsey, B. D. *J. Med. Chem.* **2008**, *51*, 1068–1072; (b) Yang, W.; Gao, X.; Wang, B. *Med. Chem. Res.* **2003**, *23*, 346–368.
6. (a) Ebdrup, S.; Jacobsen, P.; Farrington, A. D.; Vedso, P. *Bioorg. Med. Chem.* **2005**, *13*, 2305–2312; (b) Raghavendra, M. P.; Prakash, V. *J. Agric. Food Chem.* **2002**, *50*, 6037–6041; (c) Garner, C. W. *J. Biol. Chem.* **1980**, *255*, 5064–5068.
7. Decicco, C. P.; Nelson, D. J.; Luo, Y.; Shen, L.; Horiuchi, K. Y.; Amsler, K. M.; Foster, L. A.; Spitz, S. M.; Merrill, J. J.; Sizemore, C. F.; Rogers, K. C.; Copeland, R. A.; Harpel, M. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2561–2564.
8. For recent examples of synthetic methodologies used to obtain boron-containing compounds, see: (a) Qiu, D.; Mo, F.; Zheng, Z.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 5474–5477; (b) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701–17703; (c) Chen, I.; Kanai, M.; Shibasaki, M.

*Org. Lett.* **2010**, *12*, 4098–4101; (d) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704–6716. and references cited therein.
9. Kielbasinski, P.; Albrycht, M.; Zurawinski, R.; Mikolajczyk, M. *J. Mol. Catal. B: Enzym.* **2006**, *39*, 45–49.
10. (a) Andrade, L. H.; Barcellos, T. *Org. Lett.* **2009**, *11*, 3052–3055; (b) Andrade, L. H.; Barcellos, T.; Santiago, C. G. *Tetrahedron: Asymmetry* **2010**, *21*, 2419–2424.
11. (a) Hollmann, F.; Arends, I. W. C. E.; Buehler, K.; Schallmey, A.; Bühler, B. *Green Chem.* **2011**, *13*, 226–265; (b) Schrittwieser, J. H.; Sattler, J.; Resch, V.; Mutti, F. G.; Kroutil, W. *Curr. Opin. Chem. Biol.* **2011**, *15*, 249–256; (c) Fischer, T.; Pietruszka, J. *Top. Curr. Chem.* **2010**, *297*, 1–43; (d) Voss, C. V.; Gruber, C. C.; Kroutil, W. *Synlett* **2010**, *7*, 991–998; (e) Matsuda, T.; Yamanaka, R.; Nakamura, K. *Tetrahedron: Asymmetry* **2009**, *20*, 513–557; (f) Goldberg, K.; Schroer, K.; Lütz, S.; Liese, A. *Appl. Microbiol. Biotechnol.* **2007**, *76*, 237–248; (g) Moore, J. C.; Pollard, D. J.; Kosjek, B.; Devine, P. N. *Acc. Chem. Res.* **2007**, *40*, 1412–1419; (h) de Wildeman, S. M. A.; Sonke, T.; Schoemaker, H. E.; May, O. *Acc. Chem. Res.* **2007**, *40*, 1260–1266; (i) Kroutil, W.; Mang, H.; Edegger, K.; Faber, K. *Curr. Opin. Chem. Biol.* **2004**, *8*, 120–126.
12. (a) Edegger, K.; Gruber, C. C.; Poessl, T. M.; Wallner, S. R.; Lavandera, I.; Faber, K.; Niehaus, F.; Eck, J.; Oehrlein, R.; Hafner, A.; Kroutil, W. *Chem. Commun.* **2006**, 2402–2404; (b) Stampfer, W.; Kosjek, B.; Moitzi, C.; Kroutil, W.; Faber, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1014–1017; (c) de Gonzalo, G.; Lavandera, I.; Faber, K.; Kroutil, W. *Org. Lett.* **2007**, *9*, 2163–2166.
13. Karabec, M.; Łyskowski, A.; Tauber, K. C.; Steinkellner, G.; Kroutil, W.; Grogan, G.; Gruber, K. *Chem. Commun.* **2010**, *46*, 6314–6316.
14. (a) Wolberg, M.; Hummel, W.; Wandrey, C.; Müller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4306–4308; (b) Schubert, T.; Hummel, W.; Müller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 634–637.
15. Wrackmeyer, B. *Prog. NMR Spectrosc.* **1979**, *12*, 227.