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# A chiral 1,3,2-dioxaborolane derived from a natural diterpene for asymmetric reduction of prochiral ketones

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**Abstract:** The application of a chiral 1,3,2-dioxaborolane, for the sulfide complex-mediated asymmetric reduction of prochiral ketones at room temperature, are described. The *B*-methoxy-dioxaborolane was synthesized from 2α,3α-dihydroxycativic acid, a labdane-type diterpene isolated from aerial parts of Baccharis scandens DC. Very good chemical yields (85-97%) and high enantioselectivities (62-96% ee), were obtained.

**Keywords:** Asymmetric reductions; chiral 1,3,2-dioxaborolane; 2α,3α-dihydroxycativic acid.

## 1. Introduction

Asymmetric reduction of ketones into enantiomerically pure or highly enriched chiral alcohols is the key chiral building block for many important pharmaceuticals.[1] In this way, the development of chiral reagents to perform reductions with high enantioselectivity has attracted much attention.

During the last decade, numerous boron reagents are employed in asymmetric synthesis.[2,3] Under appropriate conditions, a boron moiety can form covalent bonds with diols, creating 5- or 6-membered cyclic boronate esters, such as 1,3,2-dioxaborolanes and 1,3,2-dioxaborinanes.[4] They have proven themselves to be efficient chiral reagents in many reactions such as reduction of ketones , oxime ethers and asymmetric aldol condensation.[5-7] In addition, oxazaborolidines have been reported as efficient catalysts for enantioselective reduction of ketones.[8]

On the other hand, introduction of chirality in organic molecules through the use of chiral reagents plays a key role as synthetic tool in organic chemistry. Natural products isolated from plants are of particular interest because they can often mediate significant levels of stereoselection. Accordingly, boron reagents derived from chiral terpenes as α-pinene have proved to be very valuable in asymmetric synthesis.[9]

Continuing with our studies on chiral auxiliaries derived from natural products we describe the chiral properties of 2-methoxy-1,3,2-dioxaborolane, tested in the borane-mediated asymmetric reduction of prochiral ketones.[10] The chiral borate was prepared from 2α,3α-dihydroxycativic acid, a labdane-type diterpene isolated from aerial parts of *Baccharis scandens* DC. The borane-dimethyl

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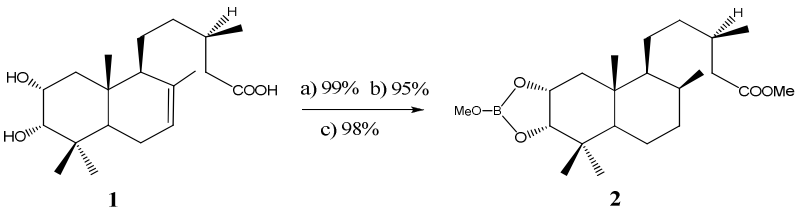
sulfide complex was used as the hydride source. The corresponding optically active alcohols were achieved in high chemical yields and good enantioselectivities.

## 2. Results and discussion

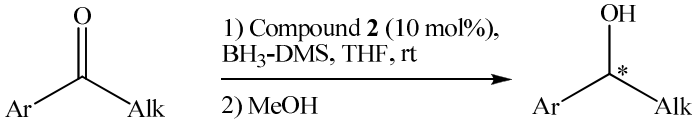
The genus *Baccharis* is one of the largest genus of the Asteraceae family with more than 500 species distributed throughout the North and South American continents. From aerial parts of *B. scandens* DC., a specie that grows in the semi-arid western region of Argentina, was isolated 2α,3α-dihydroxycativic acid (**1**).[11] Boronated **2** was prepared from labdane-type diterpene **1** in three steps, using the procedures previously reported (Scheme 1).[10]




**1** **2**

**Scheme 1:** Preparation of **2**. Reagents and conditions: (a) $CH_2N_2$, 0 °C, ether, 99%; (b) $H_2$ (Pd/C), MeOH, 95% ; (c) $B(OMe)_3$, toluene, reflux, 8 h., 98%.

In order to study their chiral properties, 2-methoxy-1,3,2-dioxaborolane (**2**) was employed *in situ* in the borane-mediated asymmetric reduction of prochiral ketones and 10 mol% of **2** were applied at room temperature (Scheme 2).




**Scheme 2:** Typical borane-dimethyl sulfide mediated asymmetric reduction of alkyl aryl ketones.

Next, dioxaborolane (**2**) was treated with various alkyl aryl ketones (**3-11**) and the corresponding optically active alcohols (**12-20**) were obtained (Figure 1). Excellent chemical yields and high enantiopurity were achieved. The results are shown in Table 1.

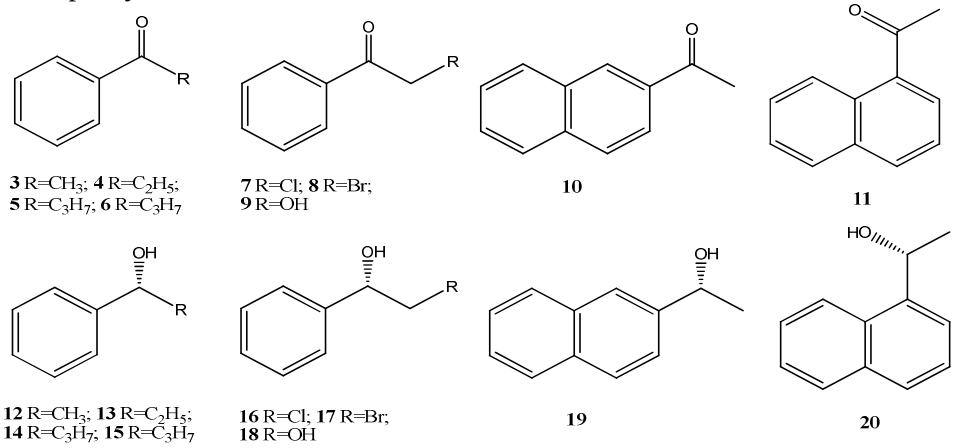



**Figure 1:** Structures of ketones and optically active secondary alcohols

**Table 1:** Asymmetric reduction of prochiral ketones **3-11** with $BH_3.Me_2S$ in the presence of 10 mol% of dioxaborolane **2**

| Entry | Ketone | Product | *ee* (%) | Conf. | Yielde (%) |
|---|---|---|---|---|---|
| 1 | **3** | **12** | 64[a] | *R*[c] | 93 |
| 2 | **4** | **13** | 64[a] | *R*[c] | 94 |
| 3 | **5** | **14** | 63[a] | *R*[c] | 87 |
| 4 | **6** | **15** | 62[a] | *R*[c] | 85 |
| 5 | **7** | **16** | 88[b] | *S*[d] | 93 |
| 6 | **8** | **17** | 90[b] | *S*[d] | 90 |
| 7 | **9** | **18** | 84[b] | *S*[d] | 95 |
| 8 | **10** | **19** | 96[b] | *R*[d] | 98 |
| 9 | **11** | **20** | 94[b] | *R*[d] | 97 |

[a] Enantiomeric excesses were determined by chiral HPLC (Daicel Chiralcel OD-H column); [b] Enantiomeric excesses were determined by capillary chiral GC; [c] Absolute configurations were determined by comparison of optical rotation with those described in the literature; [d] Absolute configurations were determined by comparison of retention times by chiral GC analyses (Supelco β-DEX 120 column);[e] Isolated yield.

Initial studies were focused in the asymmetric reduction of ketones **3**-**6**. The reduction of **3** proceeded to give (*R*)-1-phenylethanol (**12**) in 93% yield and with 64% enantiomeric excess (entry 1).[10] Compounds **4**-**6** with a ethyl, propyl and isopropyl group, as part of the side chain, afforded the *R*-alcohols **13**-**15**, with moderate to good enantioselectivities (64%, 63%, 62%) and good chemical yields (94%, 87%, 85%), respectively (entries 2-4).[12-14]

Next, ketones **7**-**9** bearing electronegative atoms were investigated under the same reaction conditions. Compounds **7**-**8**, carrying chloro or bromine atoms in alpha position, gave the alcohols **16**-**17** (*S*-form) in high enantioselectivities (up to 88%) and very good chemicals yields (up to 90%) (entries 5-6).[15,16] In addition, 2-hydroxyacetophenone (**9**) was converted to the corresponding (*S*)-alcohol **18** with good enantioselectivity (84%) and chemical yield (95%) (entry 7).[17,18]

Finally, as shown in Table 1, the asymmetric reduction of compounds ketones **10**-**11**, with a naphthyl group as substituent, gave excellent chemical yields and even better enantioselectivities. The corresponding *R*-alcohols **19**-**20**, were obtained in high enantioselectivity (96%, 94%) and very good yield (98%, 97%) (entries 8-9).[19,20]

These results suggested an influence of the electronics effects in the control of enantioselectivities, previously observed for the oxazaborolidine-catalyzed asymmetric reduction borane reduction of ketones.[21] Chemical transformations of 2-methoxy-1,3,2-dioxaborolane (**2**) in order to extend its utility effectively and improve the enantioselectivity for some substrates, in the borane-mediated asymmetric reduction of chiral ketones, are in progress.

## 3. Conclusion

The borane-dimethyl sulfide mediated reduction of prochiral ketones (**3**-**11**) using chiral auxiliary **2** proved to be stereoselective at room temperature. Compound **2** was synthesized from 2α,3α-dihydroxycativic acid, a natural diterpene isolated from *Baccharis scandens* DC. Very good chemical yields (85-97%) and high enantioselectivities (62-96% *ee*), were obtained. The influence of electronic effects in the control of enantioselectivity, previously reported for the oxazaborolidine, has been observed.

## 4. Experimental

Ketones **3**-**11**, borane-dimethyl sulfide and trimethylboroxine were obtained from Aldrich Chemical Co. All reactions were carried out under a dry nitrogen atmosphere. Purity of all reagents was checked by NMR spectroscopy. Distilled toluene was used. THF was freshly distilled over sodium before use. CC was performed on silica gel G 70–230 mesh. $^1$H NMR spectra were recorded in

$CDCl_3$ at 200.13 MHz on a Bruker AC-200 (TMS, internal standard). Optical rotations were obtained on a Perkin-Elmer 341 polarimeter. Enantiomeric excesses were determined by HPLC (Daicel Chiralcel OD-H column) or by CG (Supelco β-DEX 120 column).

**Synthesis of 2-methoxy-1,3,2-dioxaborolane** (**2**)**:**

2α,3α-dihydroxycativic acid (**1**) (45 mg/500 g plant) was isolated from aerial parts of *B. scandens* DC. Compound **2** was synthesized using the procedures previously reported and their structure was confirmed by IR and NMR spectral data [10].

**Typical procedure for the asymmetric reduction of ketones 3-11:**

To a THF (1.0 mL) solution of **2** (0.05 mmol) was added 5M $BH_3.Me_2S$ (0.5 mmol). After being stirred at room temperature for 10 min, the solution of ketones **3-11** (0.5 mmol) in THF (2 mL) was added via syringe pump over 1 h. The reaction mixture was stirred for 5 h at room temperature and quenched with MeOH (1 mL). Solvent was removed under reduced pressure. The residue was flash chromatographed though a small pad of silica gel using *n*-hexane/ethyl acetate (9:1) as solvent.

***(R)-1-Phenylethanol (12):*** Colorless oil. Yield: 93%; $^1$H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.38-7.26 (m, 5H), 4.90 (q, *J* = 6.5 Hz, 1H), 3.89 (s, 1H), 1.44 (d, *J* = 6.5 Hz, 3H); *ee* 64%; $[\alpha]_D^{25}$= +24.9° (*c* 0.77, $CHCl_3$);[10] retention time: Chiralcel OD-H column, 0.4 mL/min, 254 nm, *n*-hexane/i-PrOH (95:5), $t_1$ (*R*-isomer): 16.6 min, $t_2$ (*S*-isomer): 20.3 min).

***(R)-1-Phenylpropanol (13):*** Colorless oil. Yield: 94%; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 4.60 (t, *J* = 6.5 Hz, 1H), 1.92-1.70 (m, 2H), 1.87 (br s, 1H), 0.94 (t, *J* = 7.5 Hz, 3H); *ee* 64%; $[\alpha]_D^{25}$= +28.1° (*c* 0.82, $CHCl_3$);[12] retention time: Chiralcel OD-H column, 0.5 mL/min, 254 nm, *n*-hexane/EtOH (95:5), $t_1$ (*R*-isomer): 14.4 min, $t_2$ (*S*-isomer): 16.2 min).

***(R)-2-Methyl-1-phenylpropanol (14):*** Colorless oil. Yield: 87%; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H); 4.36 (d, *J* = 6.6 Hz, 1H), 1.96 (m, 1H), 1.84 (br s, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H); *ee* 63%; $[\alpha]_D^{25}$= +14.27° (c 2.01, Et2O);[13] retention time: Chiralcel OD-H column, 0.5 mL/min, 254 nm, *n*-hexane/i-PrOH (98:2), $t_1$ (*S*-isomer): 25.4 min, $t_2$ (*R*-isomer): 28.8 min).

***(R)-1-Phenylbutanol (15):*** Colorless oil. Yield: 85%; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.34-7.11 (m, 5H), 4.60 (dd, *J* = 7.5, 5.8 Hz, 1H), 1.88-1.50 (m, 3H), 1.47-1.00 (m, 2H), 0.86 (t, *J* = 7.5 Hz, 3H); *ee* 62%; $[\alpha]_D^{25}$ = +41.1° (*c* 0.89, $CHCl_3$);[14] retention time: Chiralcel OD-H column, 0.1 mL/min, 254 nm, *n*-hexane/i-PrOH (97:3), $t_1$ (*S*-isomer): 14.5 min, $t_2$ (*R*-isomer): 18.3 min).

***(S)-1-Phenyl-2-chloroethanol (16):*** Colorless oil. Yield: 93%; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.41–7.43 (m, 5H), 4.90 (dd, *J* = 8.8, 3.6 Hz, 1H), 3.74 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.63 (dd, *J* = 11.1, 8.8 Hz, 1H), 2.57 (s, 1H); *ee* 88%; $[\alpha]_D^{25}$ = +41.8 (*c* 0.93, $CHCl_3$);[15] retention time: Supelco β-DEX 120 column, $T_{inlet}$ = $T_{det}$ = 240 °C; $T_{start}$ = 120 °C, 2°C/min (program); $t_1$ (*S*-isomer): 25.3 min, $t_2$ (*R*-isomer): 27.8 min).

***(S)-1-Phenyl-2-bromoethanol (17):*** Colorless oil. Yield: 90%; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.38–7.33 (m, 5H), 4.93 (dd, 1H, *J* = 8.9, 3.4 Hz), 3.64 (dd, *J* = 10.4, 3.4 Hz, 1H), 3.55 (dd, *J* = 10.4, 8.9 Hz, 1H), 2.32 (s, 1H); *ee* 90% *ee*; $[\alpha]_D^{25}$ = + 37.6 (*c* 0.84, $CHCl_3$);[16] retention time: Supelco β-DEX 120 column, $T_{inlet}$ = $T_{det}$ = 240 °C; $T_{start}$ = 110 °C (isothermal); $t_1$ (*R*-isomer): 18.7 min, $t_2$ (*S*-isomer): 19.3 min).

***(S)-1-Phenylethane-1,2-diol (18):*** Colorless oil. Yield: 95%; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 4.83 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.76-3.67 (m, 2H), 2.62 (br s, 1H), 2.44 (br s, 1H); *ee* 84%; $[\alpha]_D^{25}$ = +76.7 (*c* 0.30, $CHCl_3$);[17,18] retention time: Supelco β-DEX 120 column, $T_{inlet} = T_{det}$ = 240 °C; $T_{start}$ = 120 °C, 40 °C isotherm for 120 min, 4 °C/min ramp to 140 °C; 140 °C isotherm for 120 min, $t_1$ (*S*-isomer): 159.26 min, $t_2$ (*R*-isomer): 159.88 min).

***(R)-1-(2-naphthyl)ethanol (19):*** White solid. Yield: 98%; mp 67-69 °C; $^1$H NMR (200 MHz, $CDCl_3$) δ 8.20-8.11 (m, 1H), 7.90-7.82 (m, 1H), 7.80 (d, *J* = 7.0 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.60-7.44 (m, 3H), 5.79-5.60 (m, 1H), 1.98 (bs, 1H), 1.70 (d, *J*= 6.4 Hz, 3H); *ee* %96; $[\alpha]_D^{25}$ = +71.5° (*c* 0.95, $CHCl_3$);[19] retention time: Supelco β-DEX 120 column, $T_{inlet} = T_{det}$ = 250 °C; $T_{start}$ = 140 °C (isotherm); $t_1$ (*R*-isomer): 59.9 min, $t_2$ (*S*-isomer): 62.2 min).

***(R)-1-naphthylethanol (20):*** White solid. Yield: 97%; mp 64-66 °C; $^1$H NMR (200 MHz, $CDCl_3$) δ 7.81-7.78 (m, 3H), 7.42-7.52 (m, 3H), 7.25 (bs, 1H), 5.08 (q, *J* = 6.5 Hz, 1H), 1.94 (bs, 1H), 1.60 (d, *J* = 6.5 Hz, 3H); *ee* %94; $[\alpha]_D^{25}$= +36.2° (*c* 0.78, $CHCl_3$);[20] retention time: Supelco β-DEX 120 column, $T_{inlet} = T_{det}$ = 250 °C; $T_{start}$ = 150 °C (isotherm); $t_1$ (*R*-isomer): 27.8 min, $t_2$ (*S*-isomer): 28.9 min).

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