

Enantioselective reduction of prochiral aryl ketones using a novel chiral auxiliary derived from a labdane diterpene

Diego A. Cifuentes* and Carlos E. Tonn

INTEQUI-CONICET, Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luis, Chacabuco y Pedernera, 5700 San Luis, Argentina

E-mail: cifuentes@unsl.edu.ar

Dedicated to Professor Oscar S. Giordano

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Abstract

A novel chiral 2-methoxy-1,3,2-dioxaborolane derived from 2 α ,3 α -dihydroxycativic acid, a labdane-type diterpene isolated from aerial parts of *Baccharis scandens* DC., is reported as a highly effective chiral auxiliary. This compound has been successfully used in the borane dimethyl sulfide complex-mediated asymmetric reduction of prochiral aryl ketones at room temperature. Very good chemical yields (up to 89%) and high enantioselectivities were obtained.

Keywords: Asymmetric reductions, chiral 1,3,2-dioxaborolane, 2 α ,3 α -dihydroxycativic acid, labdane-type diterpene

Introduction

Stereoselective reduction of prochiral ketones to their corresponding enantiopure secondary alcohols is a key step in the preparation of a variety of pharmaceutical products.¹ Introduction of chirality in organic molecules through the use of chiral reagents is a valuable synthetic tool in organic chemistry. As such, the development of chiral auxiliaries or catalysts to perform reductions with high enantioselectivity has attracted much attention. New methods such as asymmetric transfer hydrogenation,² metal catalyzed hydrogenations,³ enzymatic reactions⁴ and the use of metal hydride transfer reagents,⁵ have been reported.

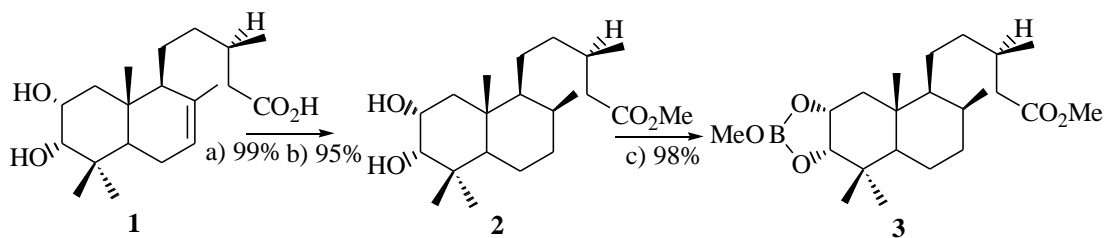
The use of chiral boron reagents has gained importance during the last decade,⁶ and some oxazaborolidines function as excellent catalysts for enantioselective borane reduction of prochiral ketones.⁷ In addition, 1,3,2-dioxaborolanes and 1,3,2-dioxaborinanes are well known as chiral reagents in many regio-, stereo- and enantioselective reactions.^{8,9}

On the other hand, numerous chiral auxiliaries and catalysts are derived from natural sources. Natural products isolated from plants are of particular interest because they can often mediate significant levels of stereoselection. In this way, boron reagents derived from chiral monoterpenes are useful in asymmetric synthesis;¹⁰ versatile pinane-based reagents have been successfully applied to many chiral transformations.¹¹

In this paper we describe the synthesis and the chiral properties of a novel 2-methoxy-1,3,2-dioxaborolane employed in borane-mediated asymmetric reduction of prochiral ketones. The 5-membered cyclic chiral borate was prepared from 2 α ,3 α -dihydroxycaticic acid, a labdane-type diterpene isolated from aerial parts of *Baccharis scandens* DC. and trimethoxyborane. The borane-dimethylsulfide complex was used as the hydride source. The corresponding optically active alcohols were achieved in high chemical yields (89-99%) and good enantioselectivities (64-98% *ee*). Additionally, the effect of chiral auxiliary-substrate ratio and temperature on the enantioselectivity is discussed.

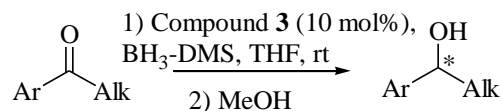
Results and Discussion

From aerial parts of *B. scandens* DC., a species that grows in the semi-arid western region of Argentina, was isolated 2 α ,3 α -dihydroxycaticic acid (45 mg/500 g plant) (**1**).¹² Methylation of the dihydroxycaticic acid **1** with diazomethane followed by Pd-catalyzed hydrogenation yielded the methyl ester **2**. The corresponding 2-methoxy-1,3,2-dioxaborolane **3** was synthesized in situ from the methyl ester **2** with trimethoxyborane in dry toluene at reflux for 8 h (Scheme 1). Its structure was supported by IR, ¹H and ¹³C NMR spectral data.^{13,14}



Scheme 1. Reagents and conditions: (a) CH₂N₂, 0 °C, Et₂O; (b) H₂ (Pd/C), MeOH; (c) B(OMe)₃, PhMe, reflux, 8 h.

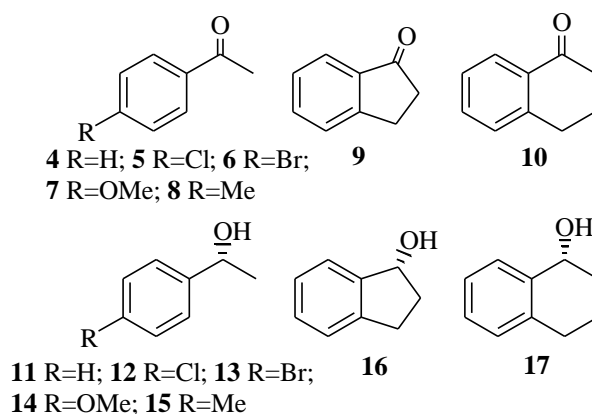
In order to study the potential of this boronate ester **3** in the borane-mediated asymmetric reduction, we selected a series of alkylaryl ketones **4-10** as substrates. The dioxaborolane **3** (10 mol %) was applied, without isolation, in the borane dimethylsulfide complex-mediated asymmetric reduction (Scheme 2).



Scheme 2. Typical borane dimethylsulfide complex-asymmetric reduction of alkylaryl ketones.

The corresponding optically active *R*-alcohols **11-17** were isolated in excellent chemical yields and good enantiopurity for sterically hindered ketones (Table 1).

Table 1. Results of enantioselective reduction of prochiral ketones **4-10** using 2-methyl-1,3,2-dioxaborolane **3**



Entry	Ketone	<i>ee</i> (%)	Conf.	Yield ^e (%)	Product
1	4	64 ^a	<i>R</i> ^d	93	11
2	5	91 ^a	<i>R</i> ^d	89	12
3	6	93 ^a	<i>R</i> ^d	94	13
4	7	89 ^a	<i>R</i> ^d	91	14
5	8	90 ^a	<i>R</i> ^d	92	15
6	9	95 ^b	<i>R</i> ^c	98	16
7	10	96 ^b	<i>R</i> ^c	98	17

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

We first carried out the asymmetric reduction of acetophenone **4** in the presence of 10 mol % of chiral dioxaborolane **3** with borane dimethylsulfide in THF at room temperature. The reduction of **4** proceeded to give (*R*)-1-phenylethanol **11** in 93% yield and with 64% enantiomeric excess (entry 1).¹⁵

Next, haloketones **5** and **6** derived from acetophenone were investigated under the same reaction conditions. Compounds **5** and **6** carrying, chlorine or bromine atoms at C-4 of the aryl

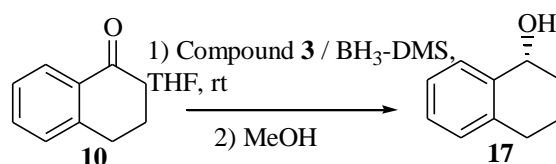
group, gave the alcohols **12** and **13** (*R*-form), respectively with moderate to good enantioselectivities (up to 91%) and good chemical yields (up to 89%) (entries 2 and 3).¹⁵

p-Methoxyacetophenone **7** was converted to the corresponding (*R*)-alcohol **14** with good enantioselectivity (89%) and chemical yield (91%) (entry 4).¹⁶ Compound **8** with a methyl substituent at the 4-position on the aryl ring provided the *R*-alcohol **15** in high enantioselectivity (90%) and very good yield (92%) (entry 5). Finally, the asymmetric reduction of the cyclic aryl ketones **9** and **10** under the same conditions gave excellent chemical yields (up to 97%) and even better enantioselectivities (Table 1). Reduction of 1-indanone **9** proceeded smoothly to give (*R*)-2,3-dihydro-1*H*-inden-1-ol **16** in high enantioselectivity (*ee* 95%, entry 6)¹⁶ and reduction of α -tetralone **10** produced the corresponding (*R*)-alcohol **17** with the best enantioselectivity (96%) (entry 7).¹⁷

In order to determine the minimum amount of reagent required to obtain the maximum selectivity, the reduction of α -tetralone **10** was performed with varying amounts (2, 5, 7 and 10 mol %) of chiral 2-methyl-1,3,2-dioxaborolane catalyst **3** (Table 2).

The results show that there is only marginal dependence of the *ee* from the amount of chiral catalyst. In addition, we also studied the effect of reaction temperature on *ee* and chemical yield (Table 3).

Table 2. Asymmetric reduction of α -tetralone **10** with varying amounts of chiral auxiliary **3**



Entry	Compound 3 (mol %)	Yield ^a (%) 17	Enantiomeric purity ^b (%) 17
1	2	98	90
2	5	97	90
3	7	97	92
4	10	98	96

^a Chemical yields of isolated product. ^b Enantiomeric excesses determined by chiral HPLC using the Chiralcel OD-H column.

Table 3. Effect of temperature on enantioselectivity of reduction of α -tetralone **10** using **3** (10 mol %)

Entry	Temperature (°C)	Yield ^a (%) 17	Enantiomeric purity ^b (%) 17
1	-78	45	50
2	-10 to 0	60	77
3	rt (25)	98	96
4	50	20	88

^a Chemical yields of isolated product. ^b Enantiomeric excesses were determined by chiral HPLC using the chiral column, Chiralcel OD-H.

Interestingly, room temperature seems optimal for the asymmetric reductions using compound **3** as the borane-coordinating auxiliary. The auxiliary may not be stable at 50 °C and at -78 °C the auxiliary formation may be too slow.¹⁸

Conclusions

The asymmetric reduction of prochiral ketones **4-10** using a new chiral auxiliary, 2-methoxy-1,3,2-dioxaborolane **3**, in the borane reduction was studied. The catalyst was derived from 2 α ,3 α -dihydroxycativic acid, a natural product isolated from the aerial parts of *Baccharis scandens* DC. Steric and/or electronic factors were discussed. In the cyclic aryl ketones series, compound **3** reduced 1-indanone **9** and α -tetralone **10** in excellent *ee* (95 and 96% *ee*, respectively). Aryl methyl ketones derived from acetophenone showed good chemical yields and moderated to good enantioselectivities. In addition, the effect of temperature and amount of chiral reagent on the enantioselectivity of the reduction were also reported.

Experimental Section

General. Ketones **1-8**, borane-dimethylsulfide and trimethoxyborane were obtained from Aldrich Chemical Co. All reactions were carried out under a dry nitrogen atmosphere. The purity of all reagents was checked by NMR spectroscopy. Dry toluene was used. THF was freshly distilled over sodium before use. CC was performed on silica gel G 70–230 mesh. ¹H NMR spectra were recorded in CDCl₃ at 200.13 MHz, whereas ¹³C NMR spectra were obtained at 50.23 MHz on a Bruker AC-200 using TMS as an internal standard. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter, and IR spectra were recorded on a Bruker IFS-2S spectrometer. Enantiomeric excesses were determined by HPLC with Daicel Chiralcel OD-H column or by CG with Supelco β -DEX 120 column.

Isolation procedure. From aerial parts of *B. scandens* DC., was isolated 2 α ,3 α -dihydroxycativic acid (**1**) (45 mg/500 g plant) using CC on silica gel G 70–230 mesh eluting with *n*-hexane, *n*-hexane/EtOAc with increasing polarity mixtures and EtOAc/MeOH (97:3).

Synthesis of 2-methoxy-1,3,2-dioxaborolane (3). Methylation with diazomethane and Pd-catalyzed hydrogenation of **1** produced **2**. To stirred mixture of compound **2** (17.7 mg, 0.05 mmol) in dry toluene (1 mL) in a three necked flask was added trimethoxyborane [B(OMe)₃] (0.01 mL, 0.1 mmol) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred and heated under reflux for 8 h. The reaction was monitored by TLC. After compound **3** was consumed, the excess B(OMe)₃ was evaporated off. Yield 98%. Amorphous

solid; $[\alpha]_D^{25} = -39.9$ (c 0.77, CHCl_3); IR (ν_{max} , cm^{-1}) = 1978, 1644, 1389, 1360, 1323, 1165. ^1H NMR (300 MHz, CDCl_3) δ 0.79 (3H, s, C-20-Me), 0.89 (3H, s, C-18-Me), 0.92 (3H, d, $J = 7$ Hz, C-17-Me), 0.97 (3H, d, $J = 7.1$ Hz, C-16-Me), 0.99 (3H, s, C-19-Me), 1.55 (1H, m, C-1 α -H), 1.55 (1H, m, C-5-H), 1.86 (1H, m, C-1 β -H), 2.28 (2H, d, $J = 7.3$ Hz, C-14-H), 3.50 (1H, brs, C-3-H), 3.65 (3H, s, $-\text{CO}_2\text{Me}$), 3.75 (3H, s, $-\text{OMe}$), 4.12 (1H, ddd, $J = 10.3, 6.0, 4.4$ Hz, C-2-H). ^{13}C NMR (75 MHz, CDCl_3) δ 14.3 q (C-20), 20.0 q (C-16), 21.8 q (C-18), 21.8 q (C-17), 23.1 t (C-6), 23.3 t (C-7), 24.9 t (C-11), 28.0 q (C-19), 31.1 d (C-13), 37.8 s (C-10)*, 38.1 s (C-4)*, 39.2 t (C-12), 39.6 t (C-1), 41.3 t (41.3), 42.8 d (C-5), 51.3 q (OMe), 51.9 q (OMe), 54.6 d (C-8), 54.8 d (C-9), 67.7 d (C-2), 79.0 d (C-3), 171.8 q (C=O), * (exchanges).

Typical procedure for the asymmetric reduction of ketones (1-8)

To a THF (1 mL) solution of dioxaborolane **3** (0.132 mg, 0.10 mmol) prepared above was added 2M $\text{BH}_3\cdot\text{Me}_2\text{S}$ (28 μL , 0.30 mmol). After being stirred at room temperature for 10 min, the solution of acetophenone **4** (120 μL , 1 mmol) in THF (2 mL) was added via syringe pump over 1 h. The reaction mixture was stirred for 5 h at room temperature. The reaction mixture was quenched with MeOH (1 mL). Solvent was removed under reduced pressure. The residue was flash chromatographed through a small pad of silica gel using *n*-hexane/ethyl acetate (9:1) as solvent.

(R)-1-Phenylethanol (11). Colorless oil in 93% yield; ^1H NMR (CDCl_3) δ 1.44 (3H, d, $J = 6.52$ Hz), 3.89 (1H, s), 4.52–4.85 (1H, m), 7.26–7.38 (5H, m). Enantiomer determination of **11**: 64% *ee* based on chiral HPLC [Daicel 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]. $[\alpha]_D^{25} = +24.9$ (c 0.77, CHCl_3).^{17,19}

(R)-1-(4-Chlorophenyl)ethanol (12). Colorless oil in 89% yield. ^1H NMR (CDCl_3) δ 1.43 (3H, d, $J = 6.34$ Hz), 2.34 (1H, s), 4.82 (1H, q, $J = 6.34$ Hz), 7.25–7.30 (4H, m). Enantiomer determination of **12**: 91% *ee* based on chiral HPLC [Daicel Chiralcel OD-H, 0.4 mL/min, 254 nm, *n*-hexane/*i*-PrOH, (95:5), t_1 (*R*-isomer): 30.0 min, t_2 (*S*-isomer): 28.9 min]. $[\alpha]_D^{25} = +20.5$ (c 0.74, CHCl_3).¹⁹

(R)-1-(4-Bromophenyl)ethanol (13). Colorless oil in 94% yield. ^1H NMR (CDCl_3) δ 1.44 (3H, d, $J = 6.28$ Hz), 2.35 (1H, s), 4.80 (1H, q, $J = 6.28$ Hz), 7.45–7.50 (4H, m). Enantiomer determination of **13**: 93% *ee* based on chiral HPLC [Daicel Chiralcel OD-H column, 0.4 mL/min, 254 nm, *n*-hexane/*i*-PrOH, (95:5), t_1 (*R*-isomer) = 31.0 min, t_2 (*S*-isomer) = 29.1 min]. $[\alpha]_D^{25} = +27.1$ (c 0.85, CHCl_3).¹⁹

(R)-1-(4-Methoxyphenyl)ethanol (14). Colorless oil in 91% yield. ^1H NMR (CDCl_3) δ 1.49 (3H, d, $J = 6.30$ Hz), 1.83 (1H, s), 3.80 (3H, s), 4.86 (1H, s), 6.88–7.31 (4H, m). Enantiomer determination of **14**: 89% *ee* based on chiral GC [Supelco β -DEX 120 column, 40–180 $^\circ\text{C}$, programming rate = 2.0, t_1 (*R*-isomer) = 66.2 min, t_2 (*S*-isomer) = 67.0 min]; HPLC (Daicel Chiralcel OD-H column, 0.3 mL/min, *n*-hexane/*i*-PrOH (95:5), t_1 (*R*-isomer) = 36.8 min, t_2 (*S*-isomer) = 41.8 min). $[\alpha]_D^{25} = +39.4$ (c 0.82, CHCl_3).¹⁷

(R)-1-(4-Methylphenyl)ethanol (15). Colorless oil in 92% yield. ^1H NMR (CDCl_3) δ 1.34 (3H, d, $J = 6.34$ Hz), 2.23 (3H, s), 2.39 (1H, s), 4.69 (1H, q, $J = 6.34$ Hz), 7.03 (2H, d, $J = 7.81$ Hz),

7.12 (2H, d, $J = 7.81$ Hz). Enantiomer determination of **15**: 90% *ee* based on chiral GC [Supelco β -DEX 120 column, 40–180 °C, programming rate = 2.0, t_1 (*R*-isomer) = 54.7 min, t_2 (*S*-isomer) = 56.2 min]. $[\alpha]^{25}_D = +31.4$ (c 0.79, CHCl₃).¹⁹

(R)-1-Indanol (16). Colorless oil in 98% yield. ¹H NMR (CDCl₃) δ 0.41 (m, 1H, C8-H), 1.87 (1H, m, C8-H), 2.75 (1H, m, 1H), 2.99 (1H, m, C9-H), 5.16 (1H, t, $J = 6.2$ Hz, C1-H); 7.15–7.19 (3H, m, Ar), 7.35 (1H, d, $J = 5.6$ Hz, Ar). Enantiomer determination of **16**: 95% *ee* based on chiral GC [Supelco β -DEX 120 column, 40–180 °C, programming rate = 2.0, t_1 (*R*-isomer) = 66.2 min, t_2 (*S*-isomer) = 67.0 min]; HPLC [Daicel Chiralcel OD-H column, 0.3 mL/min, *n*-hexane/*i*-PrOH (95:5), t_1 (*R*-isomer) = 36.8 min, t_2 (*S*-isomer) = 41.8 min]. $[\alpha]^{25}_D = -79.5$ (c 0.09, CHCl₃).¹⁶

(R)-1,2,3,4-Tetrahydronaphthalen-1-ol (17). Colorless oil in 98% yield. ¹H NMR (CDCl₃) δ 1.64 (1H, m, C10-H), 1.87 (1H, m, C10-H), 2.20 (1H, m, C9-H), 2.75 (1H, m, C9-H), 2.85 (1H, m, C-8-H), 2.99 (1H, m, C8-H), 4.96 (1H, t, $J = 6.2$ Hz, C1-H), 7.10–7.22 (3H, m, Ar), 7.38 (1H, d, $J = 5.6$ Hz, Ar). Enantiomer determination of **17**: 96% *ee* based on chiral GC [Supelco β -DEX 120 column, 80 °C, 10 min; 5 °C/min to 110 °C, 8 min; and 15 °C/min to 160 °C, 11 min. Enantiomer retention times: t_1 (*R*-isomer) = 28.3 min, t_2 (*S*-isomer) = 28.7 min]. $[\alpha]^{25}_D = -20.1$ (c 0.75, CHCl₃).¹⁹

Acknowledgements

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