[(*E*)-γ-(1,3,2-Dioxaborinanyl)allyl]diisopinocampheylborane, an Exceptional Reagent for the Stereo- and Enantioselective Synthesis of *anti*-1-Alkene-3,4-diols via a Masked α-Hydroxyallylboration

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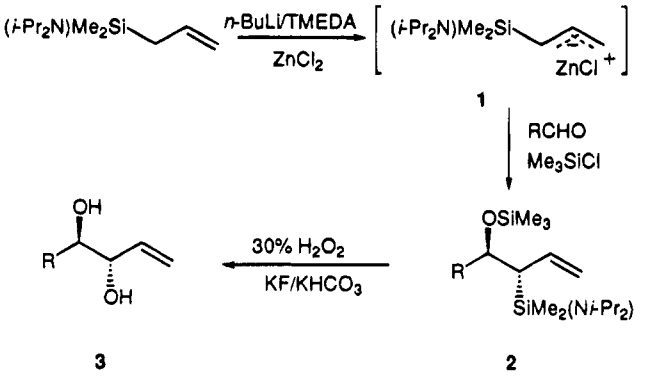
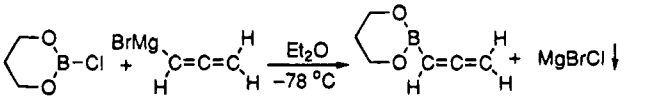
Over the past few years, asymmetric allyl- and crotylboron reagents have proven their value for the conversion of aldehydes into homoallylic alcohols of high optical purity.[1] A number of terpene-[2] and tartrate[3]-based allyl- and crotylboron reagents have been developed, and the importance of these reagents for the synthesis of 4-hydroxy-1-alkenes and 4-hydroxy-3-methyl-1-alkenes in high enantiomeric and diastereomeric purities has been successfully demonstrated.

An interest in extending the synthesis to polyhydroxylated natural products led us to examine the behavior of the corresponding (γ-alkoxyallyl)boron reagents, readily prepared via metalation of methyl allyl ether. The intramolecular coordination between oxygen and the metal fixes in the intermediate the (*Z*)- configuration of the reagent. Accordingly, the addition to aldehydes proceeds with excellent *syn* selectivities to provide the corresponding *syn* 1-alkene-3,4-diols.[4] Unfortunately, the synthesis of *anti* diols has proven to be more difficult owing to the problems encountered in the synthesis and the configurational instability of the corresponding (*E*)-alkoxyallyl anion precursors.[5] However, Ito and coworkers recently reported an indirect methodology using a zinc reagent obtained via the metalation of allyl(diisopropylamino)dimethylsilane (**1**), as a "masked" α-hydroxyallyl anion equivalent, reacting with aldehydes regio- and stereoselectively to form the *anti*-3-silyl-1-alken-4-ols (**2**), which are further transformed into *anti*-1-alkene-3,4-diols (**3**) by the oxidation of the carbon–silicon bond with hydrogen peroxide in the presence of fluoride ion (Scheme 1).[6] Roush *et al.*[7] and Barrett *et al.*[8] have developed asymmetric versions of this method for the synthesis of chiral *anti*-1-alkene-3,4-diols, using tartrate- and α-pinene-based chiral auxiliaries, respectively.

Scheme 1



We envisioned that an (*E*)-allylborane reagent with a *B* atom at the γ-position, on reaction with aldehydes and subsequent oxidation, would give the *anti*-1-alkene-3,4-diols. We report herein the successful development of a new chiral allylboron reagent, [(*E*)-γ-(1,3,2-dioxaborinanyl)allyl]diisopinocampheylborane (**7**), for the synthesis of *anti*-1-alkene-3,4-diols in high diastereo- and enantiomeric purities. We developed a simple route to the desired γ-substituted reagent starting from *B*-allenyl-(1,3,2-dioxaborinane) (**4**). Allenylboronate **4** is conveniently prepared in high yield by treating allenylmagnesium bromide (**6**) with *B*-chloro(1,3,2-dioxaborinane) (**5**) (eq 1).[9]



(1)

The key step in the preparation of the reagent **7** is the hydroboration of reagent **4** with Ipc_2BH. Gratifyingly, the hydroboration of the allenylboronate **4** with $^dIpc_2BH$[10] is quite facile in ether at 0 °C, complete in 1 h. The reagent **7** reacts readily with representative aldehydes to provide the corresponding dibora species **8**. Oxidation of **8** without isolation using alkaline hydrogen peroxide gives the desired *anti*-1-alkene-3,4-diols (**3**) in excellent yield and high diastereo- and enantioselectivities (Scheme 2, Table 1).

This method benefits from the following attributes. (i) Hydroboration of **4** with Ipc_2BH provides the corresponding (*E*)-allylic reagent **7**. The reaction is highly stereoselective as is evident from the ^1H NMR spectrum.[11] (ii)

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(9) To a solution of **5** (see ref 17) (50 mmol) in 100 mL of diethyl ether at −78 °C was added, allenylmagnesium bromide (50 mmol) (see ref 18) over 30 min. Magnesium salts precipitated out, and the reaction mixture was brought to room temperature. The supernatant ether layer was transferred to another flask with a double-ended needle, the solvents were pumped off, and the product was isolated by distillation of the resultant solution. The product **4** was obtained in a yield of 3.7 g (65%), bp 110–112 °C (80 mmHg).

(10) $^dIpc_2BH$ of 99% ee was prepared from the hydroboration of commercially available α-pinene and $BH_3{\cdot}SMe_2$: Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.

(11) The ^1H NMR spectrum of the allylic reagent **7** showed the following signals in the olefinic region: δ 6.65 (dt, J = 17.5 Hz, 7.77 Hz, 1H) and 5.23 (d, J = 17.5 Hz, 1H). The coupling constant values of the olefinic protons are in full agreement with the literature values reported for the compound (*E*)-$PhMe_2SiCH{=}CHCH_2B(OCHCO_2i\text{-}Pr)_2$ (see ref 7c). The ^1H NMR spectrum of the intermediate **7** is included with the supporting information.

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Scheme 2

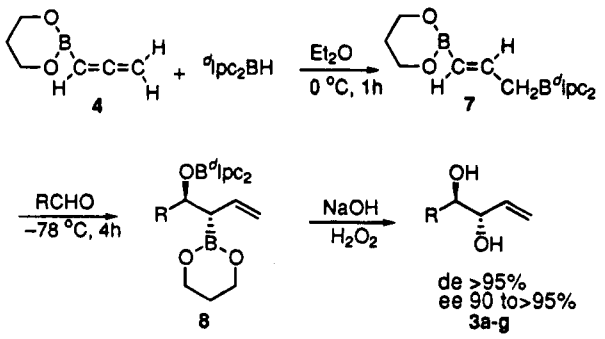

Table 1. *anti*-1-Alkene-3,4-diols from the Reaction of 7 with Representative Aldehydes

aldehyde	product	% yield[a,b]	% ee	confign
CH_3CHO	**3a**	75	91.6[c] (90)[f]	*3S,4R*[f]
CH_3CH_2CHO	**3b**	67	89.5[c]	*3S,4R*[g]
c-$C_6H_{11}CHO$	**3c**	70	94[c] (95)[f]	*3S,4R*[c]
PhCHO	**3d**	76	>95[d]	*3S,4R*[g]
PhCHO	**3e**	80	>95[d]	*3R,4S*[e]
$(CH_3)_3CCHO$	**3f**	59	>95[d]	*3S,4R*[g]
CH_2=$CHCHO$	**3g**	63		meso

[a] Isolated yield of the product after chromatography and hydroboration involved ^{d}Ipc$_2$BH, unless otherwise mentioned. [b] Only *anti*-diols were observed in the ^{1}H NMR spectrum of the crude product. [c] Determined using the chiral capillary column (Chiraldex-GTA). [d] Determined from the ^{1}H NMR of the corresponding di-Mosher esters. [e] Hydroboration involved ^{l}Ipc$_2$BH. [f] Based on specific rotation values. $[\alpha]^{23}_D$ −12.65° (*c* 1.17, $CHCl_3$) observed for **3a** (lit. $[\alpha]^{23}_D$ −9.7° (*c* 0.81, $CHCl_3$) for 69% ee)[7c] and $[\alpha]^{23}_D$ +16.175° (*c* 0.95, $CHCl_3$) observed for **3c** (lit. $[\alpha]^{23}_D$ +12.3° (*c* 2.3, $CHCl_3$) for 72% ee).[7c] [g] Based on analogy with **3a** and **3c.**

Allylic boron reagents undergo rapid, stereocontrolled addition to aldehydes with allylic rearrangement.[2] Indeed, the reaction of dialkylallylborane reagents with aldehydes is essentially instantaneous at −78 °C.[12] (iii) α-Pinene-based chiral reagents are highly enantioselective in allylboration reactions, and the ready availability of the chiral auxiliary in both antipodal forms makes this an especially convenient reagent.[1] (iv) The configuration of the double bond in the reagent **7** was established to be (*E*) by spectroscopic examination. Such derivatives are believed to undergo allylboration of aldehydes via a cyclic transition state to provide the corresponding *anti* products.[1f,7,8] (v) Oxidation of the C−B bond with alkaline hydrogen peroxide to the corresponding alcohol is stereoretentive and high yielding.[13]

All of the transformations following eq 1, from hydroboration through oxidation, can be carried out in a single pot, by successive addition of the appropriate reagents to the reaction mixture.[14] The product diols **3a−g** are obtained in good overall yield following column chromatography. The diastereomeric excess of the products in each case is established to be >95% from the ^{1}H NMR spectrum of the diol.[15] The relative stereochemistry of the diols **3d−g** is confirmed to be *anti* from the chemical shift and *J* values for the CH(OH)CH(OH) protons (3−5 Hz) in the 300 MHz ^{1}H NMR spectrum. The assignment of relative stereochemistries for the diols **3a−c** is determined from the chemical shift and *J* values of CH(OH)CH=CH_2 protons (3−5 Hz) in 300 MHz ^{1}H−^{1}H decoupling experiments. The assignment of the *anti* configuration of the diols is also confirmed by the formation of the pure meso product, with specific rotation of 0.00°, in product **3g** from the allylboration of acrolein (compare with the high rotation realized for the *syn* isomer[4]).

The enantioselectivity achieved in the reaction is determined from the ^{1}H NMR spectra of the derived di-Mosher esters (**3c−f**).[16] In the case of **3a,b**, the enantioselectivity is established by chiral capillary GC of the diacetate. The absolute stereochemistry of the diols **3a** and **c** is established to be *3S,4R* by comparing the specific rotations of the diols with values of Roush *et al.*[7c] The absolute stereochemistry of the diols **3b−f** is assigned based upon analogy with the known examples **3a** and **3c**. The results agree with the absolute stereochemical bias previously observed for all α-pinene derived reagents.[1,2]

It is clear from these results that the reagent **7** is highly diastereoselective and enantioselective in its reaction with aldehydes providing the corresponding *anti*-1-alkene-3,4-diols. In conclusion, this development provides a simple and convenient method for the synthesis of chiral *anti*-1,2-diols with simultaneous formation of a carbon−carbon bond.

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Supporting Information Available: Compound characterization data for compounds **4**, **7**, and representative diols (15 pages).

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(14) The preparation of **3c** is representative: to a stirred suspension of ^{d}Ipc$_2$BH (2.85 g, 10 mmol) in ether (20 mL) was added **4** (1.23 g, 10 mmol) at 0 °C with stirring continued for 1 h. Dissolution of the suspended ^{d}Ipc$_2$BH indicated the completion of the hydroboration. The reaction mixture was cooled to −78 °C, and cyclohexanecarboxaldehyde (0.9 g, 8 mmol) was added dropwise. Stirring was continued for 4 h at −78 °C, and the reaction mixture was warmed slowly to 0 °C. The reaction mixture (inert atmosphere) was oxidized by adding aqueous 3.0 M NaOH (7.0 mL) and 30% H_2O_2 (3.5 mL). After the addition was complete, the reaction mixture was stirred at 25 °C for 4 h. The organic phase was separated, and the aqueous phase was extracted with ether (2 × 25 mL). The combined organic phases were dried over anhyd $MgSO_4$ and purified by column chromatography (silica gel, hexane/ether, 3/1) to yield 1.0 g (76%) of diol **3c**.
(15) The relative stereochemical assignments for the anti diols were determined by comparisons of chemical shift in the ^{1}H NMR data observed with that reported for the corresponding racemic diols. See: (a) Dana, G.; Chuche, J.; Monot, M.-R. *Bull. Soc. Chem. Fr.* **1967**, 3308. (b) Figeys, H. P.; Gelbcke, M. *Bull. Soc. Chim. Belg.* **1974**, *83*, 381.
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