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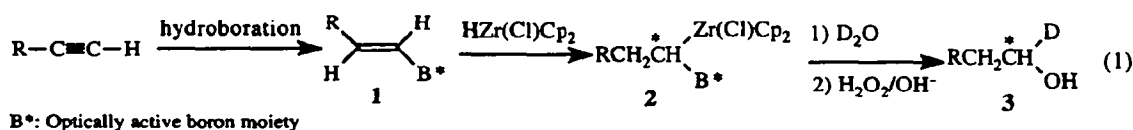
**Diastereoselective Hydrozirconation of Optically Active 1-Alkenyl Boryl Derivatives:  
A Conversion of 1-Alkynes to Optically Active 1-Deuterio Primary Alcohols**

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**Abstract:** Three types of optically pure 1-alkenyl boranes derived from monoterpenes, 1,2-diols and 1,2-amino alcohols were used for the study of diastereoselective hydrozirconation. *N*-Neopentyl oxazaborolidine derivatives were found to give excellent diastereoselectivity. Optically active 1-deuterio primary alcohols (80-93% ee) were obtained with this new type of asymmetric reaction.

Although hydrozirconation has widely been used in organic synthesis,<sup>1</sup> little attention has been paid to asymmetric hydrozirconation. Recently we have reported the preparation and synthetic application of the new boron-zirconium 1,1-bimetallic reagents obtained by hydrozirconation.<sup>2</sup> In our continuing studies on the synthesis and utility of boron-zirconium bimetallic reagents, we were interested in exploring asymmetric hydrozirconation to synthesize optically active boron-zirconium bimetallics. To prepare these compounds, we selected to take advantage of the ease with which optically active boron reagents can be prepared from optically active alkenes, 1,2-diols or 1,2-amino alcohols. In this report we describe our initial results with asymmetric synthesis by diastereoselective hydrozirconation.<sup>3</sup> This diastereoselective reaction is, to our knowledge, the first example of asymmetric hydrozirconation (eq 1).



The reaction was standardized with 1-hexyne. Based on the cost and availability of optically active ligands, three types were explored: monoterpenes, 1,2-diols and 1,2-amino alcohols (Table I). Monoterpene-derived 1-alkenyl boranes were prepared from 1-hexyne and a monoterpene hydroborating reagent. The monoterpene hydroborating reagents was obtained by hydroboration of a monoterpene with borane in a 2:1 mole ratio of monoterpene: BH<sub>3</sub> at 0°C followed by crystallization in the cold (-30°C) overnight. Filtration, followed by washing with cold THF, provided the pure dialkylborane. It was allowed to react (1eq) with 1-hexyne (1eq, 1M in THF, 0°C) overnight. The 1-alkenyl boronic esters were synthesized by the hydroboration of 1-hexyne (1eq, 2M in CH<sub>2</sub>Cl<sub>2</sub>) with HBBR<sub>2</sub>:SMe<sub>2</sub> (1.2eq, 2M in CH<sub>2</sub>Cl<sub>2</sub>), followed by the conversion of the intermediate dibromoboronic esters to the corresponding alkenylboronic acid (NaOH, ice, and EtOAc extraction), and esterification with a diol (1eq, MgSO<sub>4</sub>, 1:1 ether:hexanes, 25°C).<sup>2b-c</sup> The synthesis of oxazaborolidine 1-alkenyl

**Table I. 1-Deuterio-1-Hexanol Prepared by Sequential Deuterolysis and Oxidation of Boryl Zirconocene 1,1-Dimetallics**

Run	Ligand on Boron	THF			CH <sub>2</sub> Cl <sub>2</sub>			Absolute Config
		Chem Yield <sup>a</sup> %	% ee <sup>b</sup>	% Deuterium <sup>c</sup>	Chem Yield <sup>a</sup> %	% ee <sup>b</sup>	% Deuterium <sup>c</sup>	
1	diisopinocampheylborane	42	10	50	35	9	50	S
2	4-diisocaranylborane	51	5	70	47	42	80	R
3	(2R, 3R)-(-)-2,3-butanediol	95	8	90	89	20	95	R
4	1,2:5,6-Di-O-isopropylidene-D-mannitol	98	17	95	97	18	95	S
5	(1S,2S,3R,5S)-(+)-pinanediol	92	6	97	90	2	97	S
6	Diisopropyl L-tartrate	71	28	50	85	11	95	S
7	(1R,2S)-(-)-ephedrine	88	6	95	90	28	95	R
8	(1R,2R)-(-)-norpseudoephedrine	65	12	70	71	38	72	S
9	(1R,2S)-N-butyl-norephedrine	95	63	98	90	70	92	R
10	(1R,2S)-N-benzyl-norephedrine	97	28	98	92	56	93	R
11	(1R,2R)-N-butyl-norpseudoephedrine	88	11	94	85	15	87	R
12	(1R,2S)-N-neopentyl-norephedrine	90	80	85	82	51	80	R

<sup>a</sup>GC yield, with octane as an internal standard. <sup>b</sup> Estimated by <sup>1</sup>H-NMR by integration of the carbonyl proton of the MTPA ester derivatives.<sup>12</sup> <sup>c</sup> Estimated by comparison of integration between the peak of the carbonyl proton and the peak of the methoxy protons of MTPA esters using <sup>1</sup>H-NMR.

boranes **1** was accomplished by heating a mixture of the alkenyl boronic acid (prepared as above) with a 1,2-amino alcohol<sup>4</sup> (1eq) for 10 h at reflux in toluene with azeotropic removal of water.

Hydrozirconation of optically pure 1-alkenyl boranes **1** (1 eq, 0.5M) with HZr(Cl)Cp<sub>2</sub><sup>5</sup> (1.3 eq) provided optically active 1,1-bimetallics **2**. Selective cleavage of the C-Zr bond in **2** with D<sub>2</sub>O (1.5eq, ), followed by alkaline oxidation of the C-B bond (2eq, 3M NaOH; 3 eq, 30% H<sub>2</sub>O<sub>2</sub>), extraction of the resulting mixture with ether (4x10ml), and distillation of the organic layer, afforded the optically active 1-deuterio primary alcohols. Enantiomeric excess (ee) was determined by <sup>1</sup>H-NMR (400 MHz) analysis using an inverse gated decoupling sequence<sup>6</sup> on the MTPA esters.<sup>7</sup> The results are summarized in Table I.

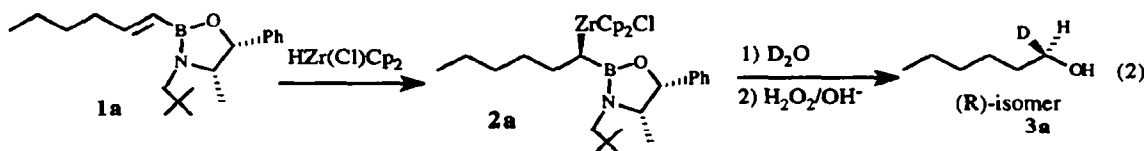
Monoterpene derivatives of alkenyl boranes **1** did not undergo complete hydrozirconation. They gave low chemical yields and low incorporation of deuterium. The 1,2-diol and 1,2-amino alcohol derivatives of **1** hydrozirconated completely and provided alcohols in relatively high chemical yields and with high deuterium incorporation. Both classes of compounds did not give high diastereoselectivity. However, the alkenyl oxazaborolidines, in addition to providing products in high chemical yields and with excellent incorporation of deuterium, also gave the best diastereoselectivity. The (1R, 2S)-ephedrine derivatives were superior to the diastereomeric (1R, 2R)-pseudoephedrine derivatives. The N-neopentyl derivative was particularly outstanding (Table I, entry 12). A number of solvents were examined. In general THF proved superior to CH<sub>2</sub>Cl<sub>2</sub>. Other solvents, i.e., hexanes (no hydrozirconation) or 1,4-dioxane offered no advantages. Therefore we selected as our standard conditions:(1R,2S)-N-neopentyl norephedrine derived oxazaborolidine and THF as the solvent. Under these conditions, highly diastereoselective hydrozirconation of various 1-alkenyl oxazaborolidines was consistently achieved (Table II).

**Table II. 1-Deuterio Primary Alcohols Prepared by Sequential Deuterolysis and Oxidation of 1,1-Bimetallics of Zirconocene and Oxazaborolidines Derived from (1*R*,2*S*)-*N*-Neopentyl-Norephedrine.**

Entry	R in Alkanyl Oxazaborolidines 1	Chem Yield <sup>a</sup> , %	% ee <sup>c</sup>	Absolute Configuration <sup>d</sup>	% Deuteration <sup>e</sup>
1	n-butyl	90	80	R	85
2	3-chloropropyl	92	85	R	98
3	cyclopentyl	89	93	R	95
4	3-phenylpropyl <sup>b</sup>	99 <sup>b</sup>	85	R	95
5	t-butyl	78	82	R	70

<sup>a</sup>GC yields, with octane as the internal standard, except entry 3 where nonane was used as the internal standard. <sup>b</sup>Crude yield, based on oxazaborolidine 1. <sup>c</sup>Estimated by the corrected integration of the peaks of the carbinyl proton of the MTPA esters, using <sup>1</sup>H-NMR.<sup>12</sup> <sup>d</sup>Assigned by analogy. See text, eq 2. <sup>e</sup>Estimated by comparison of the integration between the peak of the carbinyl proton and the peak of methoxy protons of the MTPA esters, using <sup>1</sup>H-NMR.

Oxidative cleavage of the carbon-boron bond occurs with retention.<sup>8</sup> Deuterolysis of the carbon-zirconium bond is also thought to proceed with retention.<sup>9</sup> The absolute configuration of optically active 1-deuterio-1-hexanol has been reported.<sup>10</sup> Thus by analyzing this known optically active alcohol, the absolute configuration of the 1,1-bimetallic reagent from which it was derived could be determined. Based on the data we obtained ( $[\alpha]_D^{29} +0.42$  (c 34.0, hexanes), the 1,1-bimetallic derived from 1-hexyne was assigned structure **2a** (eq 2). The absolute configurations in Tables I and II were then assigned by analogy.



Although the mechanism of this new type of asymmetric reaction is not yet understood, the assignment of structure **2a** is consistent with the approach of  $\text{HZrCp}_2\text{Cl}$  from the less hindered face of the double bond. The pseudonorephedrine derived reagents, whose double bond is more symmetrically disposed, give lower selectivities in the hydrozirconation step.

In conclusion, we have developed a highly diastereoselective hydrozirconation. A practical application is the preparation of deuterated alcohols, since 1-deuterio alcohols have great value in mechanistic studies of chemical and biochemical reactions.<sup>11</sup> The results described herein suggest that the optically active boron-zirconium 1,1-bimetallic reagents may open a new field in asymmetric synthesis. Design of optically active ligands on boron and further synthetic application of these bimetallics will be the subject of our future studies.

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## References and notes

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12. The %ee was corrected for non deuterated related peaks at  $\delta$  4.33 and 4.29 of the diastereomeric deuterated alcohol MTPA esters. The non deuterated 1-hexanol MTPA ester gave a doublet of doublets at  $\delta$  4.36, 4.34, 4.32, and 4.29 in <sup>1</sup>H NMR, Fig 1, top curve. The ratio of the signals at  $\delta$  4.36, 4.34, and 4.32, and 4.29 are consistently 1:7.56:1.21. The signal at  $\delta$  4.36 does not contribute to the peak areas of the deuterated alcohol ester. signals at  $\delta$  4.34 and 4.32 contribute to the area of  $\delta$  4.33 of the deuterated alcohol ester. The peak at  $\delta$  4.29 of the non deuterated alcohol ester obviously contributes to the peak area of the deuterated alcohol ester. Using these data, we calculated the corrected %ee by deduction of 7.56 times the area of the signal at  $\delta$  4.36 from the area of the signal at  $\delta$  4.33, and deduction of 1.21 times the area of the signal at  $\delta$  4.36 from the area of the signal at  $\delta$  4.29, Fig 1 bottom curve.

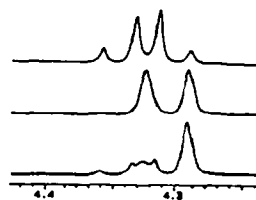


Figure 1. Top curve: <sup>1</sup>H-NMR spectrum of the carbonyl protons of non deuterated 1-hexanol MTPA ester. Center curve: <sup>1</sup>H-NMR spectrum of the carbonyl proton of the MTPA ester of racemic 1-deuterio-1-hexanol. Bottom curve: <sup>1</sup>H-NMR spectrum of the carbonyl proton of the MTPA ester of optically active 1-deuterio-1-hexanol (Table II, entry 1). All spectra were obtained using an inverse gated decoupling sequence.

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