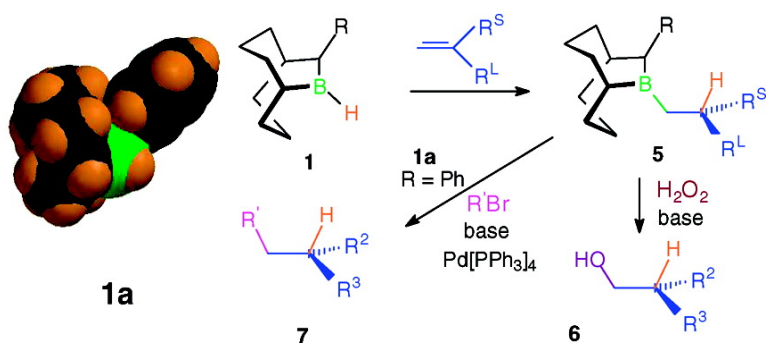Communication

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9-Borabicyclo[3.3.2]decanes and the Asymmetric Hydroboration of 1,1-Disubstituted Alkenes

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In their seminal study, Brown and Zweifel ushered in the modern era of reagent-controlled asymmetric synthesis with the hydroboration of cis-alkenes employing diisopinocampheylborane (Ipc$_2$BH, Figure 1, **A**).[1] The instability of this reagent with respect to dehydroboration, led to the development of monoisopinocampheylborane (IpcBH$_2$) (Figure 1, **B**)[2] which was found to be effective for trans- and trisubstituted alkenes. In some cases, the intermediate mixed dialkylborane dimers can be crystallized to provide enantiomerically pure organoboranes for many synthetic applications.[2b] Masamune's C_2-symmetric borolane (DMB, Figure 1, **C**) is highly selective for all of these substrates, namely cis, trans, and trisubstituted alkenes.[3] Unfortunately, none of theses reagents, including a Rh-BINAP catalyzed process,[4] is effective for the hydroboration of 2-substituted-1-alkenes (e.g., α-methylstyrene, Ipc$_2$BH, 5% ee; 2-methyl-1-butene, IpcBH$_2$, 1% ee; 2,3-dimethyl-1-butene, DMB, 1.4% ee; 2-phenyl-1-butene, catecholborane, Rh-BINAP, 46% ee;). To address this nearly 50 year-old challenge, we wish to report the preparation of the 10-substituted-9-bora-bicyclo[3.3.2]decanes (10-R-9-BBD-H, **1**) and their unique behavior in the asymmetric hydroboration of 1,1-disubstituted alkenes.

The BBD-pseudoephedrine complexes **2a** (R = Ph)[5a] and **2b** (R = TMS)[5b] were treated with LiAlH$_3$(OEt) producing an insoluble dialkoxyalane which was easily separated from the soluble borohydrides **3** (^{11}B NMR: **3a** δ −12.4 (t, J = 67 Hz), **3b** δ −20.0 (t, J = 67 Hz) by decantation (Scheme 1). The reagents **1** were generated by the addition of TMSCl (or MeI) to **3**. Both **1a** and **1b** form 1:1 trans adducts with pyridine (i.e., **4** ^{11}B NMR δ 5.0, 3.1, respectively). The reagents **1** differ considerably in that **1a** is completely dimeric in solution at 25 °C (^{11}B NMR δ 27.4), whereas its more crowded counterpart **1b** exists as a 3:1 mixture of monomer (^{11}B NMR δ 79) and dimer (^{11}B NMR δ 27) at room temperature.[6] Interestingly, dimer **1a** is observed by ^{13}C NMR as a 60:40 mixture of two isomeric forms (i.e., "cis/trans", see Scheme 1). It is probable that this phenomenon contributed to the fact that we were unable to obtain **1a** dimer as a crystalline compound. For this reason, we chose to freshly generate this and **1b** from **3** in the presence of the alkene to be hydroborated. Representative alkenes were examined with both **1a** and **1b** and these results are presented in Table 1.

Both **1a** and **1b** exhibit remarkable selectivity in the asymmetric hydroboration of 1,1-disubstituted alkenes. Hydroborations with **1a** are complete in <12 h at 25 °C. However, the bulkier **1b** is less reactive (α-methylstyrene (48 h), 2,3,3-trimethyl-1-butene (168 h)). Both reagents exhibit unprecedented levels of selectivity in the hydroboration of 2-methyl-1-alkenes (cf., **6f** from **1a** (78% ee), Ipc$_2$BH, 5% ee[1b]). Moreover, larger differences in the size of R$_S$ vs R$_L$ result in higher selectivity (cf., α-deuteriostyrene, **6g** from **1a** (92% ee), HOCH$_2$CHDPr from Ipc$_2$BH, 48% ee[1c]).

Other alkene types undergo selective hydroboration with **1**. Thus, the hydroboration of trans-2-butene with **1a** and **1b** produces 2-butanol **6a** in 96 and 95% ee, respectively. With cis-2-butene,
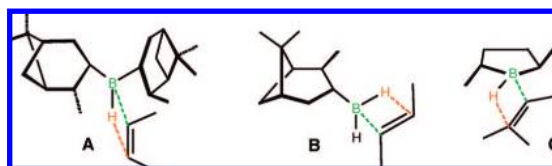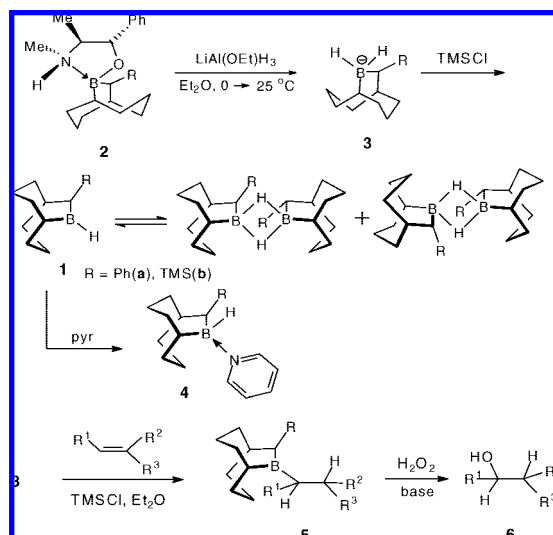

Figure 1. Asymmetric hydroborating agents.

Scheme 1

1a gives the same alcohol (32% ee) while with **1b**, the epimeric adduct is formed giving the enantiomeric form of **6a** in 84% ee. The reaction of 2-methyl-2-butene is very slow with **1b**, but it does react smoothly with **1a** (12 h, 25 °C) to produce **6b** in 74% ee.

Our explanation for these selectivities is depicted in Figure 2. For both **1a** and **1b**, the 1,1-disubstituted alkenes approach from the side opposite to the 10-R system positioning the larger alkene substituent away from this group. However, the preferred boat/chair conformations are reversed for **1a** vs **1b** with respect to the 10-R group.[5] Thus, the long C-SiMe$_3$ bond (1.92 Å) in **1b** favors the boat side of the ring syn to the TMS group, while the shorter C-Ph (1.52 Å) bond in **1a** results in ring-Ph interactions which favor the chair form syn to the 10-Ph group.[5] In the case of alkenes with α-substitution (i.e., cis, trans, and tri), for **1a**, the approaching alkene experiences a protruding boat form which exerts a major α-directive effect (vide supra). The hydroboration of trans-2-butene is highly selective because this steric effect is reinforced by those of the 10-Ph group. For cis-2-butene, these effects conflict with the ring playing the dominant role. In **1b**, the flatter chair form of the ring produces only minor interactions resulting in a process essentially directed by the 10-TMS group.

Table 1. Asymmetric Hydroboration of Representative Alkenes with **1**

borane	alkene R¹	alkene R²	alkene R³	6	yield (%)[a]	ee[b]	abs configuration[c]
1aS	Me	Me	H	a	>90	32	S
1bR	Me	Me	H	a	98	84	S
1aS	Me	H	Me	a	>90	96	S
1bR	Me	H	Me	a	95	95	R
1aS	Me	Me	Me	b	79	74	S
1aR	H	Me	Et	c	83	28	S
1bR	H	Me	Et	c	87	40	S
1aR	H	Me	i-Pr	d	97	38	S
1bS	H	Me	i-Pr	d	82	52	R
1aS	H	Me	t-Bu	e	84	92	R
1bR	H	Me	t-Bu	e	60	56	S
1aS	H	Me	Ph	f	95	78	R
1bR	H	Me	Ph	f	83	66	S
1aS	H	D	Ph	g	97	92	R
1bS	H	D	Ph	g	86	98	R
1aS	β-pinene			h	94	97[d]	1S,2R,5S
1aR	β-pinene			h	94	99[d]	1S,2R,5S
1aS	R-limonene			i	93	76[d]	4R,8R
1aR	R-limonene			i	93	22[d]	4R,8R

[a] Isolated yields of analytically pure material except for **6a** whose yields were determined by GC using an internal standard. [b] Product ee was determined by ³¹P NMR after conversion of **6** to the corresponding Alexakis esters. For some cases, analysis was accomplished through ¹³C NMR of Mosher esters derivatives. [c] Absolute configuration determined by comparison to literature values (see Supporting Information). [d] Diastereomeric excess.
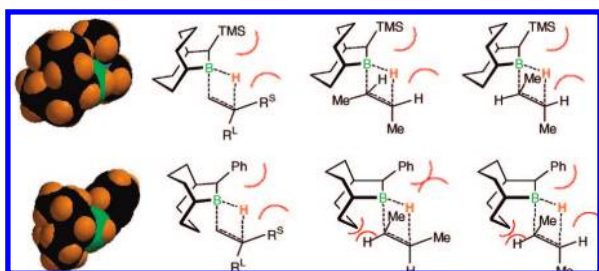

Figure 2. Possible origins of the observed selectivity in the asymmetric hydroboration of alkenes with 10-Ph-9-BBD (**1a**, bottom) and 10-TMS-9-BBD (**1b**, top). The preferred orientations for 1,1-disubstituted, cis- and trans-2-butene are illustrated above. Notice the outward protrusion of the boat form of the 10-Ph-9-BBD (**1a**) ring (α-directing for cis, trans and trisubstituted alkenes) vs the flatter chair form for **1b** with respect to the approaching alkene. MM space-filling models were generated with Spartan 06.

Chiral substrates[7] such as β-pinene can override the reagent control exhibited by **1** giving cis-myrtanol with both **1a**R and **1a**S reagents. However, with the less rigid R-limonene, the matched combination with **1a**S gives an impressive 88:12 dr.

Because of its greater rate of hydroboration compared to **1b**, we chose to employ **1a** to prepare **5a** (R¹ = H) for Suzuki couplings (Scheme 2).[8] Through this process, we can prepare nonracemic 1°-alkylboranes which generally make excellent partners for this coupling. This contrasts to the behavior of the normal products of asymmetric hydroboration, namely 2°-alkylboranes, which reduce rather than couple with the electrophilic component in this process. Further, we felt that this new chemistry would provide a reliable protocol for preparing relatively unfunctionalized compounds with optical purities that would be known from the values determined

Scheme 2
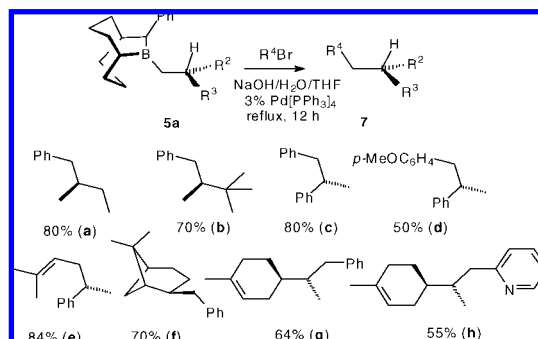
from the oxidation of **5** (i.e., **6**).[9] The eight examples which were examined are shown in Scheme 1. We selected aryl, heteroaryl, and vinyl bromides to couple with **5** producing the desired Suzuki products **7** in 50−84% yields.

The synthesis of the asymmetric hydroborating agents **1** has been reported. These reagents exhibit unprecedented selectivity in the hydroboration of 1,1-disubstituted alkenes producing **5** which can either be oxidized to give nonracemic primary alcohols **6** or coupled to electrophilic substrates through the Suzuki protocol to give **7** whose optical purities are determined by those of the organoborane precursor **5**.

Supporting Information Available: Experimental procedures, analytical data and selected spectra for **1**−**7**, and derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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