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Nonracemic Homopropargylic Alcohols via Asymmetric Allenylboration with the Robust and Versatile 10-TMS-9-borabicyclo[3.3.2]decanes†

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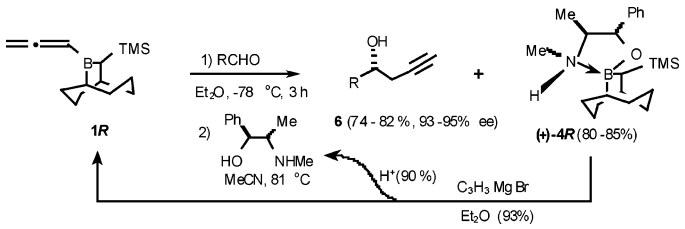
ABSTRACT



The asymmetric allenylboration of representative aldehydes with the stable, storable 1 is reported. Easily and efficiently prepared in either enantiomeric form from the air-stable crystalline 4 through simple Grignard procedures, 1 gives 6 cleanly. The latter is easily isolated in high yield and ee with predictable stereochemistry. The procedure also regenerates 4 for its direct conversion back to 1 and facilitates the efficient recovery of the pseudoephedrine. The net process is the synthetic equivalent of the asymmetric addition of allenylmagnesium bromide to aldehydes.

Asymmetric allenylboration provides a highly useful route to nonracemic homopropargylic alcohols. Although less common than its allylboration counterpart,[1] this mechanistically related S_E2' addition was first reported by H. Yamamoto, who employed chiral 1,3,2-dioxaborolanes derived from modified tartrates.[2] Corey later introduced vicinal diamine-based 1,3,2-diazaborolanes from which either *B*-allenyl or *B*-propargyl systems could be prepared from appropriate organotin precursors. These reagents proved to be highly effective for both asymmetric allenyl- and propargylboration.[3] The Grignard reagent derived from propargyl bromide is effectively used for the synthesis of these systems, in the first, to prepare alleneboronic acid and, in the second, to prepare either the propargyl- or allenyltin precursors to the *B*-allenyl- or propargyl-1,3,2-diazaborolanes, respectively. As illustrated with this second process, the clean formation of allenylmetallic reagents and their additions to carbonyl compounds can be quite challenging.[4] Both organotin and silicon derivatives provide useful stoichiometric sources of

† This work is dedicated to the memory of my mentor, the late, great Professor Herbert C. Brown, whose love of chemistry, standards of excellence, and levels of accomplishment have been profoundly influential and inspirational to me and to many others. His passing marks the end of an era.

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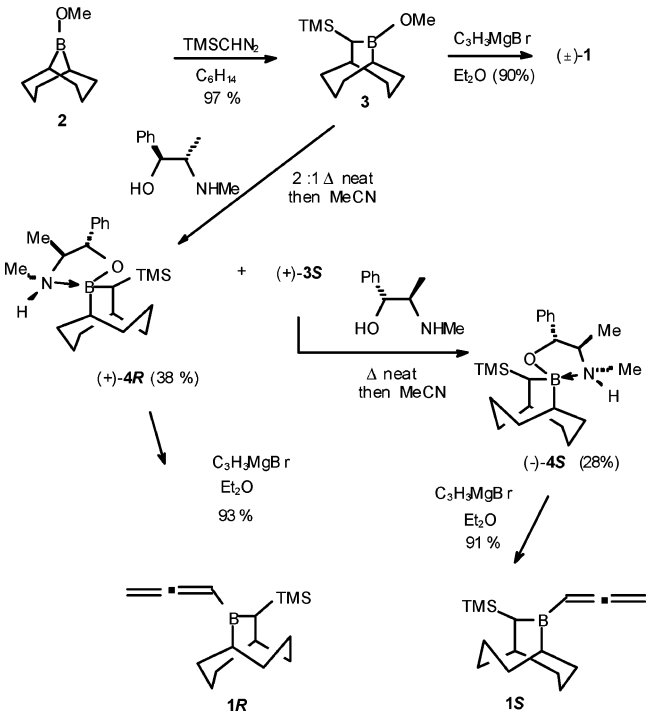
the allenylmetallic for catalytic asymmetric allenylations.[4m,n,s] For organoboranes, Zweifel observed that α-substituted allenyldialkylboranes undergo a 1,3-boratropic rearrangement to the propargyl system if the allenylboranes were allowed to thermally equilibrate at 25 °C.[5] However, this rearrangement is not observed for unsubstituted *B*-allenyl systems, and isomerically pure *B*-allenyl-9-BBN is readily prepared, free of propargylic impurities, from C_3H_3MgBr and *B*-Cl-9-BBN.[6] This reagent adds rapidly at −78 °C to both aldehydes and ketones to give racemic homopropargylic alcohols exclusively.

We felt that if more direct access to effective reagents for asymmetric allenylboration were available, new applications for the versatile homopargylic alcohols would follow.[2,7] The ideal reagent should be readily available in either enantiomeric form directly from a simple Grignard procedure. It should also be easy to isolate in pure form and be a stable reagent that can be stored indefinitely. The reagent should also be highly enantioselective, adding rapidly to aldehydes in a highly predictable manner. Moreover, the allenylboration procedures with the reagent should also be designed to recycle the chiral borane moiety by producing the precursor to this reagent. If this intermediate was also an air-stable crystalline compound, the difficulties associated with the handling of air-sensitive organoboranes could be eliminated. In a general sense, we felt that the reagent should provide the equivalent of the asymmetric addition of allenylmagnesium bromide to aldehydes. Mindful of these goals, we wish to report the synthesis of the enantiomeric *B*-allenyl-10-TMS-9-borabicyclo[3.3.2]-decanes (**1**) and their use in the asymmetric allenylboration process.

Scheme 1



Recently, we described the clean insertion of CHTMS into a ring B−C bond in **2** by $TMSCHN_2$ (10 h, C_6H_{14}, 70 °C) to afford the very stable *B*-MeO-10-TMS-9-BBD (**3**) in 97% yield after distillation (bp 80 °C, 0.10 mmHg) (Scheme 1).[8] Not only is **3** thermally stable, but also it is unusually stable, for a borinate ester, to the open atmosphere for brief periods of time (17 h, 3% oxidation). Moreover, **3** is cleanly converted to (±)-**1** with allenylmagnesium bromide in ether. The isolation of (±)-**1** in pure form is quite simple, involving only filtration, concentration, and distillation (90%, bp 88−91 °C, 0.10 mmHg) (Scheme 1).[9] To our knowledge, this is the first time that a chiral allenylborane has been isolated in pure form.[2,3]

Compound (±)-**3** is easily resolved through a modified version of the Masamune amino alcohol protocol[10] employing 0.5 equiv of (1*S*,2*S*)-pseudoephedrine (PE) in acetonitrile to give (+)-**4*R*** (38%) as a pure crystalline compound, leaving (+)-**3*S*** in solution. After concentration of the supernatant to remove the liberated methanol, 0.5 equiv of (1*R*,2*R*)-PE

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(9) We initially investigated several alternative routes to (±)-**1** including the *B*-X-10-TMS-9-BBD (X = Cl, Br)/allenyltributyltin exchange process for which the *B*-Br derivative is successful (CH_2Cl_2, 25 °C, 28 h).

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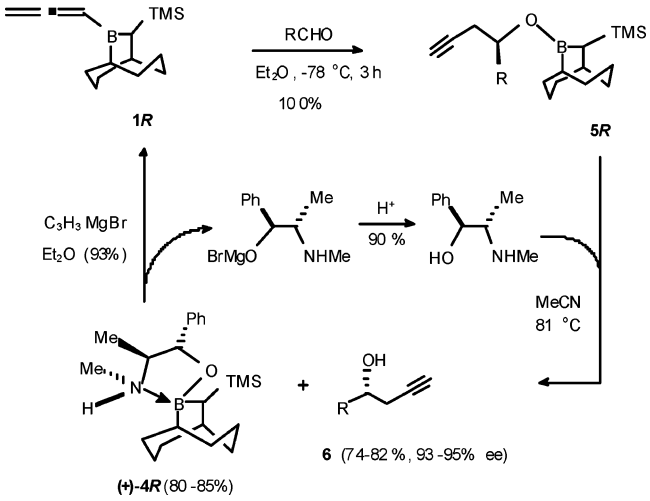
Scheme 2



was added to a fresh solution of the residue in acetonitrile, ultimately giving (−)-**4*S*** (28%), also as a pure crystalline compound. The order of addition of the enantiomeric PEs can be reversed to give, first, (−)-**4*S*** and, second, (+)-**4*R***. In this way, (±)-**3** is converted into separated enantiomerically pure components whose combined yield total 66%! These complexes are air-stable and can be stored indefinitely. In the solid state, the complex (+)-**4*R*** exists as the chelated form exhibiting both the open and closed forms in solution (^{11}B NMR (C_6D_6) δ 55.4, 17.4).[7]

Clearly, the enantiomerically pure forms of **1** could be prepared from the optically pure forms of **3**. However, a more direct route to these allenylboranes was found through the reaction of allenylmagnesium bromide with either (+)-**4*R*** or (−)-**4*S***, which cleanly produces either pure **1*R*** (93%) or **1*S*** (91%), respectively. Thus, despite the presence of the secondary amine functionality in **4**, this Masamune metathesis[9] is very clean. Moreover, the pseudoephedrine is easily recovered from the precipitated magnesium salts in 90% yield (Scheme 2). *The reagents **1** can be stored in bulk indefinitely at* −20 °C *under a* N_2 *atmosphere for subsequent use in the asymmetric allenylboration process.* The allenylboration of representative aldehydes with **1*R*** was examined at −78 °C (3 h) to provide both the corresponding homopropargylic alcohols **6** (74−82%) and the crystalline (+)-**4*R*** (80−85%) efficiently. The **1*R*** is easily directly regenerated from (+)-**4*R*** through a simple Grignard procedure (>90%) (Scheme 2, Table 1). The six representative substrates examined include aliphatic (primary, secondary, and tertiary), aromatic, α,β-unsaturated and heterocyclic aldehydes. The stable intermediate borinates **5*R***, which are formed quantitatively and are easily characterized by NMR, were treated with (1*S*,2*S*)-PE to precipitate crystalline (+)-**4*R***.[11] The product alcohols **6** were obtained through simple distillation. Their absolute configuration was assigned by comparing the sign of their optical rotations to reported values.[2,4p] Through the

(11) Attempts to substitute other amino alcohols, such as 2-amino ethanol, for PE failed to produce a crystalline precipitate.

Table 1. Allenylboration of RCHO with 1*R*

R	entry[a]	**6** (%)	$[\alpha]_D^{28}$ (*c*, MeOH)	% ee[b] (abs conf)	(+)-**4*R*** (%)
n-Pr	a	82	−28.18(2.2)	94 (*S*)	84
i-Pr	b	81	−3.45(1.2)	93 (*R*)	85
t-Bu	c	75	+45.37(1.1)	94 (*R*)	80
Ph	d	78	+11.18(1.7)	93 (*R*)	81
Vi[c]	e	74	−36.79(2.1)	94 (*R*)	82
2-furyl	f	80	−6.61(2.4)	95 (*R*)	80

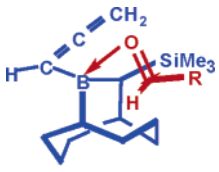
[a] All runs were made in duplicate (at least) and the **a** series was performed with both (−)-**1*R*** and (+)-**1*S***. (**6a′**, 80%, 93% ee (*R*) $[\alpha]_D^{28}$ = +28.10 (*c* 2.2, MeOH)). [b] Product ee determined by conversion to the Mosher esters and analysis by ^{13}C and ^{1}H NMR. Absolute configurations were determined from literature values and by analogy to closely related compounds. [c] Vi = vinyl.

^{1}H and ^{13}C NMR analysis of their Mosher esters, **6** was found to be formed with consistently high enantioselectivity (93−95% ee).[12]

To demonstrate further the versatility of **1** in the asymmetric allenylboration process, the enantiomeric reagent **1*S*** was examined in its addition to *n*-butyraldehyde to afford the enantiomeric (+)-**6a′** (80%, 93% ee) together with recovered (−)-**4*S*** (84%). This result is consistent with those obtained from the **1*R*** reagent and demonstrates the versatility of **1** for the preparation of both enantiomeric forms of **6**.

The chemoselectivity of **1** was examined with a 1:1:1 mixture of (±)-**1**, PhCHO, and $PhCOCH_3$ in ether at −78 °C (3 h). Only (±)-**5d** and unreacted PhCOMe were observed by ^{1}H and ^{13}C NMR. In fact, in a separate experiment, (±)-**1** failed to react with PhCOMe even at 25 °C for 1 week. Thus, the bulky **1** is even more aldehyde-selective than is its 9-BBN counterpart.

In the absence of high-level computational data, simple MM calculations[13] provide useful models for the prediction of the product stereochemistry through the relative stabilities of their diastereomeric pre-transition-state complexes. These calculations reveal that the *B*-chiral *anti*-aldehyde complex that forms *cis* to the 10-TMS group in the boat-chair form of **1*R*** (i.e., **7**) is consistently favored over any conformation



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of its *syn* and/or *trans* counterparts. This leads to the selective allenylation of the *re* face of the aldehyde with the **1*R*** reagent. For **7**, the γ-allenylic carbon is within 3.4 Å of the

(12) The C-3 (propargylic) position in the (*R*)-Mosher chloride-derived esters of **6** is consistently shifted upfield (Δδ 0.1−0.3) when compared to those from the enantiomeric alcohols. Other NMR signals were also used (see Supporting Information).

(13) Performed using the Spartan 4.0.4a GL MM program.

aldehydic carbon, well positioned for reaching the expected chairlike transition state. Any attempt to reach an alternative transition state through rotation about the B−O and B-allenyl bonds is thwarted by the TMS group, which completely blocks this pathway. Through an extensive examination of alternative complexes, the data suggests that the *anti*-aldehyde complex that forms *trans* to the 10-TMS group in the chair-chair form of **1*R*** (1.3 kcal/mol higher in energy than **7** (R = Ph)) is responsible for the formation of the minor enantiomer of **6** (∼3%).

In summary, the reagents **1** are easily prepared as stable, storable chiral allenylboranes in either enantiomeric form in high yield through simple Grignard procedures that employ the air-stable crystalline borane complexes **4**. In their allenylborations of aldehydes, the homopropargylic alcohol products **6** are produced cleanly and are easily isolated in high yield with predictable stereochemistry and consistently high ee's. The allenylation procedure developed for **1** incorporates the regeneration of **4** for its direct conversion back to **1** through a simple, highly efficient Grignard procedure that also permits the efficient recovery of the pseudoephedrine. Through these procedures, the 10-TMS-9-BBD system orchestrates the equivalent of the asymmetric addition of allenylmagnesium bromide to aldehydes.

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Supporting Information Available: Full experimental procedures, characterization data, and selected spectra for **1**−**6** and derivatives This material is available free of charge via the Internet at http://pubs.acs.org.

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