Organoborane Chemistry

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# Asymmetric Synthesis of Isomerically Pure Allenyl Boranes from Alkynyl Boranes through a 1,2-Insertion–1,3-Borotropic Rearrangement**

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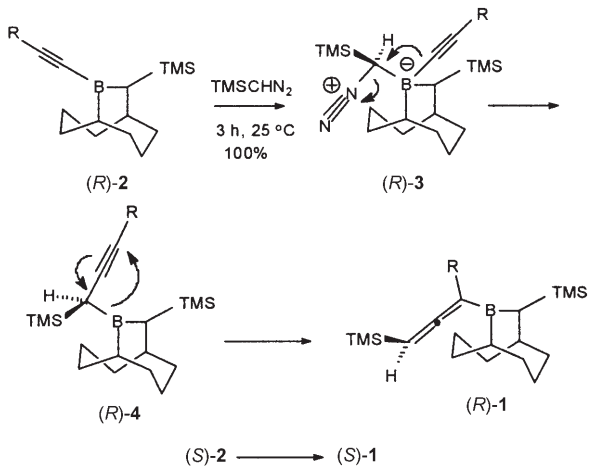
Very recently, we described a variety of new 10-trimethylsilyl-9-borabicyclo[3.3.2]decane (10-TMS-9-BBD) reagents for the asymmetric allyl-, crotyl-, allenyl-, and propargylboration of aldehydes.[1] Prepared through adaptations of known organoborane transformations, these rigid and robust trialkyl borane systems are exceptionally stable and selective. Moreover, the related 10-Ph-9-BBD reagents, which are quite effective for the related addition reactions to ketones and ketimines, can also be prepared readily.[2]

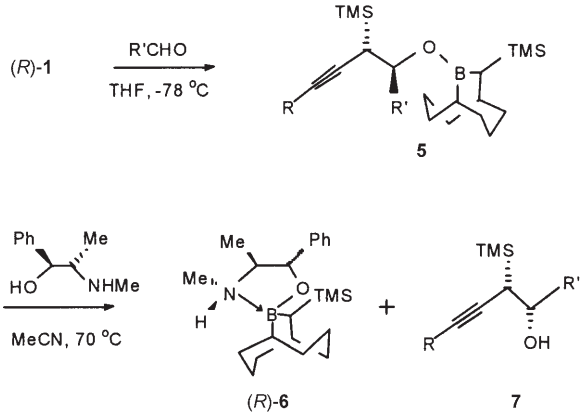
Simple Grignard procedures can be used to prepare many of these reagents, including the *B*-alkynyl 10-TMS-9-BBDs (**2**), the asymmetric Michael addition of which to *N*-acyl aldimines provides nonracemic *N*-propargyl amides.[3] On the basis of modeling studies with **2**, we envisaged the highly stereoselective insertion of $TMSCHN_2$ into the alkynyl B–C bond of **2** to give **4** via **3** (Scheme 1). An antiperiplanar 1,2-alkynyl migration (Matteson-type homologation)[4a] followed by a sterically driven suprafacial 1,3-borotropic rearrangement were expected to proceed with a minimum of TMS–TMS repulsions and ultimately convert the propargyl borane **4** into the novel chiral allenyl borane **1**.[1c,2a,4b]




***Scheme 1.*** The preparation of **1** from **2** through insertion–borotropic rearrangement. TMS = trimethylsilyl.

The thermally stable, optically pure alkynyl boranes **2** (**a**: R = Me; **b**: R = $(CH_2)_4Cl$; **c**: R = *c*-Pr; *c*-Pr = cyclopropyl) are readily prepared in either enantiomeric form through the reaction of the corresponding alkynyl Grignard reagents with the pseudoephedrine complexes **6** (96–99%). At room temperature, $TMSCHN_2$ reacts cleanly with **2** with the evolution of nitrogen to form **1** ($^{11}B$ NMR: $\delta = 78$ ppm) in 3 h. We view this process as occurring through the reversible addition of $TMSCHN_2$ to the least hindered side of **2**, followed by the insertion of CHTMS into **2** with inversion. The chiral α-borylallenes **1** are then produced in enantiomerically and diastereomerically pure form in essentially quantitative yield by a suprafacial 1,3-borotropic rearrangement (Scheme 1).

Asymmetric allenylboration[1b,2c,5] is a highly useful organoborane transformation. Compound **1** was tested as an asymmetric allenylboration reagent with representative aldehydes (Scheme 2). The addition was rapid at −78 °C (3 h), and the intermediate borinic esters **5** produced were either oxidized or converted into the pseudoephedrine complexes **6** for recycling back to **2** by the Grignard methodology. The *syn* β-TMS homopropargylic alcohols **7** were isolated in 80–96% yield with d.r. 99:1 and 94–99% *ee* (Table 1). This process is more enantioselective than allenylboration with the parent *B*-allenyl system (93–95% *ee*).[1b] The enhanced enantioselectivity can be attributed to the additional α substituent




***Scheme 2.*** Asymmetric allenylboration with **1**.

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*Table 1:* Allenylboration of R′CHO with **1**.

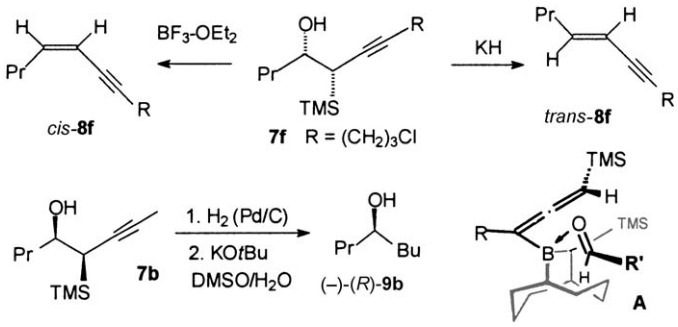
| **1** | R | R′ | Series | Yield [%][a] | d.r.[a] | *ee* [%][b] |
|---|---|---|---|---|---|---|
| (*S*)-**a** | Me | Me | **a** | 80 | 99:1 | 94 (*R*) |
| (*R*)-**a** | Me | Pr | **b** | 90 | 99:1 | 98 (*R*) |
| (*S*)-**a** | Me | *i*Pr | **c** | 89 | 99:1 | 98 (*R*) |
| (*R*)-**a** | Me | *i*Bu | **d** | 85 | 99:1 | 99 (*R*) |
| (*S*)-**a** | Me | Ph | **e** | 87 | 99:1 | 99 (*R*) |
| (*R*)-**b** | $(CH_2)_3Cl$ | Pr | **f** | 90 | 99:1 | 99 (*S*) |
| (*S*)-**c** | *c*-Pr | Pr | **g** | 96 | 99:1 | 96 (*R*) |

[a] The *anti* isomer was not detected by NMR spectroscopy for any of the alcohols **7**. In the case of **7f**, stereospecific eliminations to give **8f** were carried out to confirm its high *syn* diastereomeric purity, which was verified by $^{31}P$ NMR spectroscopic analysis of a mixture of esters derived from the four isomers of this alcohol by the method of Alexakis et al.[8] [b] The *ee* value of the product was determined by conversion into the Alexakis esters and analysis by $^{31}P$ NMR spectroscopy.[8] The products **7a–c,e,f**, of allenylboration at 25 °C were formed with 91, 98, 94, 98, and 94% *ee*, respectively.

in **1**, which increases the effective size of the allenyl group relative to that of the aldehyde (compare **A** below). When the allenylborations with **1** were conducted at 25 °C, only a modest diminution in enantioselectivity (91–98% *ee*) was observed (Table 1, footnote b). This relative insensitivity of the enantioselectivity of the process to the reaction temperature is a signature feature of the BBD reagents.[1]

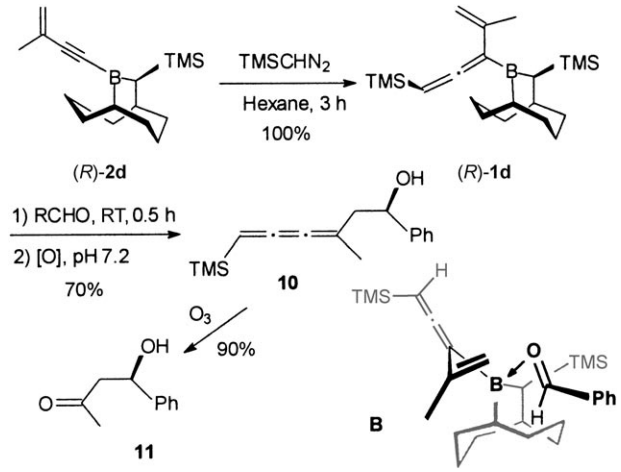
The γ-silyl group in the allenyl borane introduces a second stereogenic center in the homopropargylic alcohols **7**. In related homoallylic systems, this β-silyl substitution has been shown to provide useful functionality for further synthetic conversions.[6]

To establish the relative configuration and diastereomeric purity of **7**, acid- and base-mediated eliminations as described by Hudrlik and Peterson were conducted with **7f** as a representative example (Scheme 3).[7] These remarkably stereospecific processes produced the corresponding *cis* and *trans* alkenes **8f** ($^1H$ NMR: $J = 10.7$ and 15.8 Hz, respectively) and thus clearly revealed the absence of the *anti* diastereomer in **7f**. We also prepared **7f** independently as a mixture of diastereomers by using the 10-Ph analogue of **1b** and found that clearly resolved $^{13}C$ NMR spectroscopic signals were easily observed for the *syn* versus *anti* isomers; four clearly resolved signals were observed in the $^{31}P$ NMR spectrum of the mixture of the four esters derived from the isomers of **7f** by the protocol of Alexakis et al.[8,9] To determine the absolute configuration of **7**, we subjected **7b** to hydrogenation followed by base-mediated desilylation[10] of the saturated β-silyl alcohol to provide (−)-(4*R*)-octanol, whose configuration is known. The pre-transition-state complex **A** represents a convenient way to view the origin of the observed selectivity for this and related processes.[1–3]




*Scheme 3.* Relative and absolute configuration of **7**. DMSO = dimethylsulfoxide.

An interesting extension of the chemistry of these new organoboranes is illustrated by the conversion of **2d** into the allenyl borane (*R*)-**1d** and the reactivity of this compound, which is both an allenyl and an allyl borane. The treatment of (*R*)-**1d** with PhCHO resulted in the exclusive formation of the spectacular chiral 1,2,3-trienyl alcohol **10** (Scheme 4).




*Scheme 4.* Formation and ozonolysis of the 1,2,3-trienyl alcohol **10**.

Although this alcohol does decompose with time, it is stable to chromatography and was isolated as a single isomer, as determined by NMR spectroscopic analysis (70%, >99% *ee*).[11] The absolute configuration of **10** was determined through its conversion into the known compound (+)-(1*R*)-3-oxo-1-phenyl-1-butanol **11** by ozonolysis. The *E* configuration of the [3]cumulene was assigned on the basis of our mechanistic model for the processes involved, that is, pre-transition-state structure **B**.[11a,b]

In this study, the novel enantiomerically pure allenyl boranes **1** were synthesized from $TMSCHN_2$ and **2** through a novel silicon-mediated insertion–rearrangement process. The chemistry of these highly reactive, environmentally friendly boranes was examined in the asymmetric allenylboration of a wide range of aldehydes. Extremely high selectivities were observed, and the chiral boron moiety could be recovered efficiently and recycled. The allyl allenyl borane **1d** was found to function as an allylating agent to provide a diastereomerically pure 1,2,3-trienyl alcohol in >99% *ee*.

## Experimental Section

Synthesis of **2**: A suspension of **6** (1.19 g, 3.0 mmol) in $Et_2O$ (10 mL) was cooled to −78 °C, the alkynyl magnesium bromide (4 mL, 1.0 M in $Et_2O$) was added dropwise, and the mixture was allowed to warm to 25 °C. After 0.5 h, the reaction was cooled again to −78 °C, and TMSCl (0.8 mL) was added. The cold bath was removed 10 min after

the addition, and the solution was concentrated under vacuum by using standard techniques to prevent the exposure of the borane to the open atmosphere. The residue was washed with pentane (6 × 10 mL), and the extracts were filtered through a celite pad. The filtrate was concentrated to afford **2** in essentially quantitative yield. The compounds (±)-**2** were also prepared by a similar procedure from (±)-*B*-MeO-10-TMS-9-BBD.

Synthesis of **1**: Trimethylsilyldiazomethane (4 mmol, 2 M in hexanes) was added dropwise to a solution of **2** (2.9 mmol) in pentane (5 mL) at room temperature. After 3 h ($^{11}$B NMR (pentane): $\delta = 78$ ppm), concentration of the mixture gave **1** in quantitative yield.

Representative procedure: A solution of **1** (2.9 mmol) in THF (10 mL) was cooled to −78 °C, PrCHO (2.7 mmol) was added dropwise, and the mixture was stirred for 3 h. Oxidative workup: After the mixture had warmed to 25 °C, a phosphate buffer solution (pH 7.2, 10 mL) was added dropwise. Aqueous NaOH (2.0 mL, 3 M) and $H_2O_2$ (0.9 mL, 30 %) dropwise were also added, and the mixture was heated at reflux for 2 h. It was then extracted with brine (3 × 20 mL), and the organic phase was dried over $MgSO_4$ and filtered. The product was purified by column chromatography on silica gel (hexane/ether/$NEt_3$ 95:4:1) to give **7b** (0.48 g, 90 %). Workup with pseudoephedrine: After warming to 25 °C, the mixture was concentrated in vacuo to give the borinate **5**, which was dissolved in $CH_3CN$ (7 mL). (1*R*, 2*R*)-Pseudoephedrine was added, and the mixture was refluxed for 12 h, then cooled slowly to provide crystalline (−)-(*S*)-**6**. The crystals were washed with pentane (3 × 5 mL) and dried under vacuum to give (−)-(*S*)-**6** (0.86 g, 80 %). The supernatant was then purified by column chromatography on silica gel (hexane/ether/$NEt_3$ 95:4:1) to afford **7b** (0.48 g, 90 %).

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[1] a) C. H. Burgos, E. Canales, K. Matos, J. A. Soderquist, *J. Am. Chem. Soc.* **2005**, *127*, 8044; b) C. Lai, J. A. Soderquist, *Org. Lett.* **2005**, *7*, 799; c) E. Hernandez, J. A. Soderquist, *Org. Lett.* **2005**, *7*, 5397; see also: d) M. L. Maddess, M. Lautens, *Org. Lett.* **2005**, *7*, 3557; e) E. Hernandez, E. Canales, E. Gonzalez, J. A. Soderquist, *Pure Appl. Chem.* **2006**, *78*, 1389.

[2] a) E. Canales, K. G. Prasad, J. A. Soderquist, *J. Am. Chem. Soc.* **2005**, *127*, 11572; b) E. Canales, E. Hernandez, J. A. Soderquist, *J. Am. Chem. Soc.* **2006**, *128*, 8712; c) E. Hernandez, C. H. Burgos, E. Alicea, J. A. Soderquist, *Org. Lett.* **2006**, *8*, 4089.

[3] A. Z. Gonzalez, E. Canales, J. A. Soderquist, *Org. Lett.* **2006**, *8*, 3331.

[4] a) D. S. Matteson, *Chem. Rev.* **1989**, *89*, 1535; b) G. Zweifel, S. J. Backlund, T. Leung, *J. Am. Chem. Soc.* **1978**, *100*, 5561.

[5] a) N. Ikeda, I. Arai, H. Yamamoto, *J. Am. Chem. Soc.* **1986**, *108*, 483; b) R. Haruta, M. Ishiguro, N. Ikeda, H. Yamamoto, *J. Am. Chem. Soc.* **1982**, *104*, 7667; c) E. J. Corey, C.-M. Yu, D.-H. Lee, *J. Am. Chem. Soc.* **1990**, *112*, 878.

[6] a) W. R. Roush, P. T. Grover, X. Lin, *Tetrahedron Lett.* **1990**, *31*, 7563; b) W. R. Roush, A. N. Pinchuk, G. C. Micalizio, *Tetrahedron Lett.* **2000**, *41*, 9413; c) H. Huang, J. S. Panek, *J. Am. Chem. Soc.* **2000**, *122*, 9836.

[7] P. F. Hudrlik, D. Peterson, *J. Am. Chem. Soc.* **1975**, *97*, 1464.

[8] A. Alexakis, S. Mutti, P. Mangeney, *J. Org. Chem.* **1992**, *57*, 1224.

[9] The 10-Ph analogue of (±)-**2b** was prepared. It reacted vigorously with $TMSCHN_2$ to give two diastereomeric silyl allenyl boranes ($^{13}$C NMR: $\delta = 216.3$ and 216.4 ppm). These boranes underwent addition to PrCHO to give **7f**, the $^{13}$C NMR spectrum of which contained an additional set of alkynyl, *O*-methinyl, and TMS signals relative to that of **7f** formed from (±)-**1b**. The $^{31}$P NMR spectrum of the corresponding ester derivatives formed by the protocol of Alexakis et al.[8] contained additional signals for the esters derived from *anti*-**7f** ($\delta = 85.4$, 86.6 ppm) which are completely absent in the spectrum of the esters formed from *syn*-**7f** derived from (±)-**1b** ($\delta = 85.9$, 86.3 ppm). The formation of enantiomeric rather than diastereomeric alcohols is puzzling. We can only speculate that they may be formed from an open transition state.

[10] P. F. Hudrlik, A. M. Hudrlik, A. K. Kulkarni, *J. Am. Chem. Soc.* **1982**, *104*, 6809.

[11] a) T. Yoshida, R. M. Williams, E. Negishi, *J. Am. Chem. Soc.* **1974**, *96*, 3688; b) E. Negishi, T. Yoshida, A. Abramovitch, G. Lew, R. M. Williams, *Tetrahedron* **1991**, *47*, 343; c) K. K. Wang, B. Liu, Y. Lu, *J. Org. Chem.* **1995**, *60*, 185; d) H.-F. Chow, X.-P. Cao, M.-K. Leung, *J. Chem. Soc. Perkin Trans. 1* **1995**, 193; e) H. Kleijn, M. Tigchelaar, R. J. Bullee, C. J. Elsevier, J. Meijer, P. Vermeer, *J. Organomet. Chem.* **1992**, *440*, 329; see also: f) I. Saito, K. Yamaguchi, R. Nagata, E. Murahashi, *Tetrahedron Lett.* **1990**, *31*, 7469.

  