

# *B*-Allenyl- and *B*-( $\gamma$ -Trimethylsilylpropargyl)-10-phenyl-9-borabicyclo[3.3.2]decanes: Asymmetric Synthesis of Propargyl and $\alpha$ -Allenyl 3°-Carbinols from Ketones

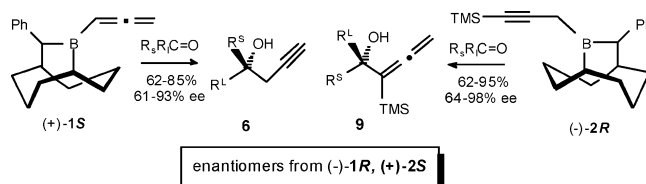
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Received June 28, 2006

## ABSTRACT



Simple and efficient Grignard procedures are reported for the syntheses of *B*-allenyl-10-(phenyl)-9-borabicyclo[3.3.2]decane (**1**) and its *B*-( $\gamma$ -trimethylsilylpropargyl) counterpart (**2**) in both enantiomeric forms. Both add selectively to ketones, providing propargyl- and  $\alpha$ -silylallenyl 3°-carbinols, respectively (i.e., **6** (61–93% ee) and **9** (64–98% ee)). The air-stable boron byproduct is efficiently recovered and recycled back to either **1** or **2**. The ozonolysis and bromination of **9** provide nonracemic  $\alpha$ -hydroxy acids and  $\gamma$ -bromopropynyl carbinols, respectively.

Recently, we reported the asymmetric allenyl- and propargylboration of aldehydes with the 10-trimethylsilyl-9-borabicyclo[3.3.2]decanes (10-TMS-9-BBDs).<sup>1</sup> These new reagents provide efficient syntheses of nonracemic propargylic and  $\alpha$ -allenyl carbinols, respectively. Moreover, the robust, rigid, and recyclable nature of the BBD ring system makes these systems highly attractive alternatives to other methods.<sup>2</sup> Neither process is known for prochiral ketones.<sup>3</sup> The success of these and related S<sub>E</sub>2' processes requires the formation of isomerically pure allenyl- or propargylborane reagents, and Grignard procedures are now available for both.

(1) (a) Hernandez, E.; Soderquist, J. A. *Org. Lett.* **2005**, *70*, 5397. (b) Lai, C.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 799. See also: (c) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044.

(2) (a) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483–486. (b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667–7669. (c) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878. (d) Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130. (e) Kulkarni, S. V.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 4125.

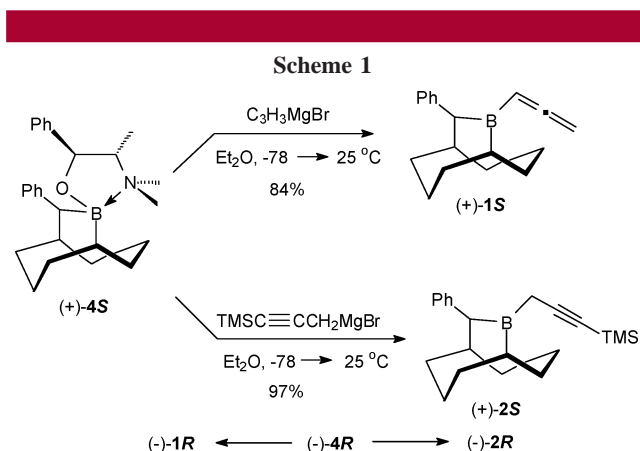
In related studies, we discovered that for asymmetric allylboration, the 10-TMS-9-BBD reagents are effective for aldehydes, whereas the corresponding 10-Ph-9-BBD reagents are effective for ketones.<sup>4</sup> We now wish to report the preparation of both enantiomerically pure forms of *B*-allenyl-10-Ph-9-BBD (**1**) and  $\gamma$ -trimethylsilyl-propargyl-10-Ph-9-BBD (**2**) and their additions to prochiral ketones for the highly selective asymmetric syntheses of propargyl- (**5**) and  $\alpha$ -allenyl- (**9**) 3°-carbinols, respectively.

The thermally stable ( $\pm$ )-*B*-MeO-10-Ph-9-BBD (**3**), readily prepared from *B*-MeO-9-BBN, serves as a very convenient precursor to both (+)-**4S** and (–)-**4R** as pure crystalline

(3) For racemic processes, see: (a) Zweifel, G.; Backlund, S. J.; Leung, T. *J. Am. Chem. Soc.* **1978**, *100*, 5561. (b) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376. (c) Wang, K. K.; Liu, C. *J. Org. Chem.* **1985**, *50*, 2578. (d) Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130. With chiral substrates, see: Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodriguez-Acebes, R. *J. Org. Chem.* **2001**, *66*, 5208.

(4) Canales, E.; Prasad, G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572.

compounds, with a combined total yield of 67%.<sup>4</sup> These complexes are air-stable and can be stored indefinitely. The reagents **1** were readily prepared in optically pure forms through the addition of allenylmagnesium bromide to the *N*-methylpseudoephedrine (NMPE) borinic ester complexes **4** (84%; Scheme 1).<sup>5</sup> The Grignard reagent derived from



3-bromo-1-TMS-1-propyne was also found to cleanly add to **4** to provide either (–)-**2R** or (+)-**2S** (97%; Scheme 1).

The asymmetric allenylboration of representative ketones was examined with **1**. Rapid reaction is observed with methyl ketones (3–12 h, –78 °C). The resulting 3°-carbinols **6** are obtained efficiently (62–85%) in high ee (61–93%; Table

**Table 1.** Allenylboration of  $R_L R_S CO$  with **1**

$R_L$	$R_S$	<b>1</b>	series	<b>6</b> <sup>a</sup> (%)	% ee <sup>b</sup> (abs config)
Ph	Me	<i>S</i>	<b>a</b>	74	91 ( <i>S</i> )
Ph	Me	<i>R</i>	<b>a</b>	85	93 ( <i>R</i> )
Ph	Et	<i>R</i>	<b>b</b>	65	76 ( <i>R</i> )
Et	Me	<i>R</i>	<b>c</b>	71	74 ( <i>S</i> )
Bu	Me	<i>S</i>	<b>d</b>	80	81 ( <i>R</i> )
<i>i</i> -Pr	Me	<i>R</i>	<b>e</b>	71	84 ( <i>R</i> )
<i>t</i> -Bu	Me	<i>S</i>	<b>f</b>	66	83 ( <i>S</i> )
TMS	Me	<i>S</i>	<b>g</b>	62	90 ( <i>R</i> )
CH <sub>2</sub> =CH	Me	<i>S</i>	<b>h</b>	64	61 ( <i>S</i> )

<sup>a</sup> The **a** series was performed with both (–)-**1R** and (+)-**1S**. The **aS**, **b**, **f**, and **h** series were conducted employing an oxidative workup. For the remaining examples, the intermediate **5** was isolated and converted to **6** and either **4** or **8** was recovered (69–81%) via the NMPE workup procedure.

<sup>b</sup> Product ee determined by conversion to the Alexakis esters<sup>6</sup> and analysis by <sup>31</sup>P NMR.

1). However, with propiophenone, the addition is much slower (2 d, 25 °C), with **5b** being produced in 76% ee. Notably, even very challenging substrates such as 2-butanone and methyl vinyl ketone give **6** with highly respectable levels of selectivities (i.e., 74 (**c**) and 61% (**h**) ee, respectively).

Encouraged by these very positive results with the allenylboration of ketones with **1**, we turned our attention to the corresponding propargylboration of representative ketones with **2**. Based on our earlier studies with the propargyl-versus allenylboration of aldehydes with the corresponding 10-TMS-9-BBD systems,<sup>1</sup> we expected even higher enantioselectivities from **2** than we had observed with **1**.

The asymmetric propargylboration of representative ketones was examined with **2** in THF at –78 °C and found to provide good to excellent yields (62–95%) of the corresponding α-allenyl 3°-carbinols **9**, with methyl ketones generally exhibiting high selectivities (78–98% ee; Table

**Table 2.** Propargylboration of  $R_L R_S CO$  with **2**

$R_L$	$R_S$	<b>1</b>	series	<b>9</b> <sup>a</sup> (%)	% ee <sup>b</sup> (abs config) <sup>c</sup>
Ph	Me	<i>S</i>	<b>a</b>	81	97 ( <i>R</i> ) <sup>d</sup>
Bu	Me	<i>S</i>	<b>b</b>	62	84 ( <i>R</i> )
<i>c</i> -C <sub>6</sub> H <sub>9</sub> <sup>e</sup>	Me	<i>S</i>	<b>c</b>	67	91 ( <i>R</i> )
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<i>R</i>	<b>d</b>	95	92 ( <i>S</i> )
<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	Me	<i>S</i>	<b>e</b>	80	98 ( <i>R</i> )
<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Me	<i>S</i>	<b>f</b>	79	98 ( <i>R</i> )
2-C <sub>4</sub> H <sub>3</sub> S <sup>e</sup>	Me	<i>S</i>	<b>g</b>	71	78 ( <i>S</i> )
2-C <sub>4</sub> H <sub>3</sub> O <sup>e</sup>	Me	<i>S</i>	<b>h</b>	82	80 ( <i>R</i> )
Ph	Et	<i>S</i>	<b>i</b>	63	64 ( <i>R</i> )

<sup>a</sup> In each case, the crystalline byproduct **8** was recovered (50–85%) using a pseudoephedrine (PE) workup (i.e., (1*R*,2*R*)-(–)-PE for (+)-**8S** and (1*S*,2*S*)-(+)-PE for (–)-**8R**). This process is both more economical and more convenient than with NMPE, which is not currently available in both enantiomeric forms. Moreover, **8** is easily converted back to **2** (>95%) through the same general Grignard procedure used for **4**. <sup>b</sup> Product ee was determined by reaction of **8** with phosphorus CDA and analysis by <sup>31</sup>P NMR. <sup>c</sup> Configuration predicted by analogy to **9a**. <sup>d</sup> Allenic alcohol **9a** was converted to the known 2-hydroxy-2-phenylpropionic acid and the sign of rotation was compared with the reported value. <sup>e</sup> 1-Cyclohexenyl, 2-thienyl, and 2-furyl.

2). Reaction times for these substrates varied considerably from 3 to 36 h for the methyl ketones. The aryl ketones,

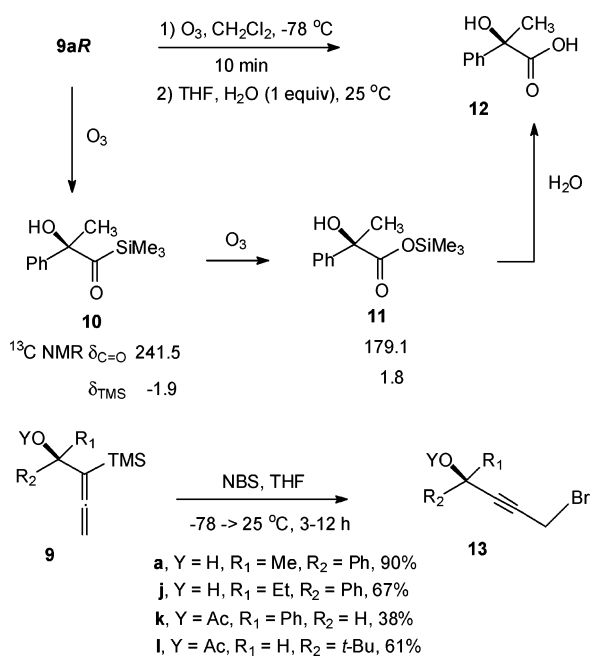
(5) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892.

(6) Alexakis, A.; Frutos, J. C.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1994**, *59*, 3326.

containing electron-withdrawing groups (i.e., Table 2, series **e** and **f**) were the slowest in this group. Even less reactive is the ethyl ketone, propiophenone, whose propargylation requires 52 h at  $-78\text{ }^{\circ}\text{C}$ . However, even highly demanding substrates, such as 2-hexanone, give **9** with high selectivity (i.e., **9b**, 84% ee).

The absolute stereochemistry for **9a** was determined by its conversion to the known atrolactic acid (**12**) through simple ozonolysis (Scheme 2). This oxidation is greatly

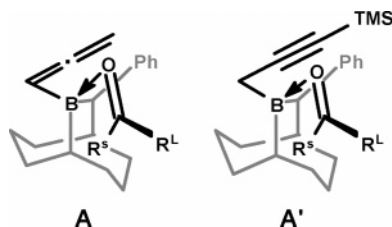
**Scheme 2**



facilitated by the  $\alpha$ -TMS substitution in **9**, which permits the ozonolysis to proceed directly to **11** through **10**.<sup>1a</sup> To

discover other potential applications for this  $\alpha$ -silylallenyl functionality, we examined the NBS-mediated bromodesilylation of **9a,j** together with two examples of *O*-Ac 2°-carbinols **9k,l**. The reactions are highly regioselective producing the corresponding propargyl bromides **13** cleanly in nonracemic form. This simple synthesis of these interesting polyfunctional compounds represents another useful feature of the TMS substitution<sup>3b,c</sup> in **2** which leads to **9**.

As previously described,<sup>4</sup> the 10-substituted-9-BBD ring clearly defines a “chiral pocket”, as illustrated in the energetically favored pre-transition state complexes **A** and **A'** (see below) for the allenyl- and propargylboration processes with the reagents **1R** and **2R**, respectively. Because BBD systems are stable, easily prepared in either enantiomerically pure form, highly reactive, environmentally friendly, recyclable, and exhibit high selectivities over a wide range of unsymmetrical ketones, their applications to the asymmetric allenyl- and propargylboration to ketones represent highly useful new processes.



**Acknowledgment.** The support of the NSF (CHE-0517194), and NIH (S06GM8102) is gratefully acknowledged.

**Supporting Information Available:** Full experimental procedures, analytical data, and selected spectra for **1**, **2**, **6**, **9–13**, and derivatives (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL061596J