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B-Allenyl- and *B*-(γ-Trimethylsilylpropargyl)-10-phenyl-9-borabicyclo[3.3.2]decanes: Asymmetric Synthesis of Propargyl and α-Allenyl 3°-Carbinols from Ketones

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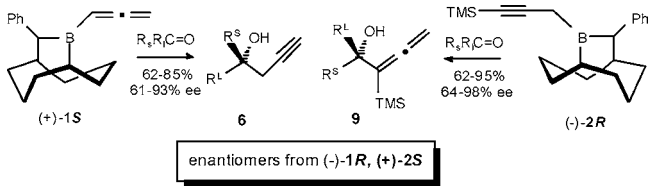
ABSTRACT



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*-(γ-trimethylsilylpropargyl) counterpart (2) in both enantiomeric forms. Both add selectively to ketones, providing propargyl- and α-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 α-hydroxy acids and γ-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).[1] These new reagents provide efficient syntheses of nonracemic propargylic and α-allenylic carbinols, respectively. Moreover, the robust, rigid, and recyclable nature of the BBD ring system makes these systems highly attractive alternatives to other methods.[2] Neither process is known for prochiral ketones.[3] The success of these and related S_E2' processes requires the formation of isomerically pure allenyl- or propargylborane reagents, and Grignard procedures are now available for both.

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.[4] We now wish to report the preparation of both enantiomerically pure forms of *B*-allenyl-10-Ph-9-BBD (**1**) and γ-trimethylsilyl-propargyl-10-Ph-9-BBD (**2**) and their additions to prochiral ketones for the highly selective asymmetric syntheses of propargyl- (**5**) and α-allenyl- (**9**) 3°-carbinols, respectively.

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

(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.

(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.

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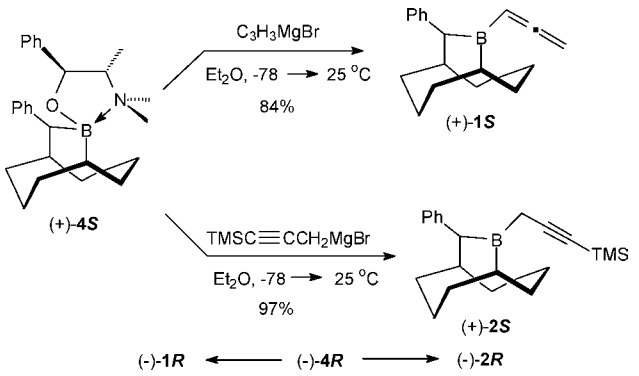
compounds, with a combined total yield of 67%.[4] These complexes are air-stable and can be stored indefinitely. The reagents **1** were readily prepared in optically pure forms through the addition of allenylmagnesium bromide to the *N*-methylpseudoephedrine (NMPE) borinic ester complexes **4** (84%;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

Scheme 1



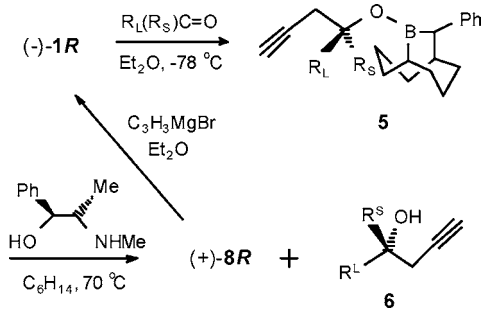
3-bromo-1-TMS-1-propyne was also found to cleanly add to **4** to provide either (−)-**2*R*** or (+)-**2*S*** (97%; Scheme 1).

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 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,[1] 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 2).

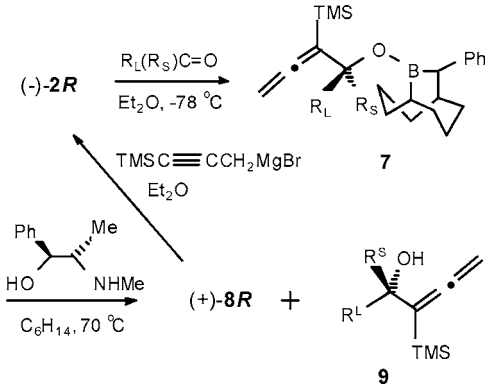
Table 1. Allenylboration of R_LR_SCO with **1**



R_L	R_S	**1**	series	**6**[a] (%)	% ee[b] (abs config)
Ph	Me	***S***	**a**	74	91 (S)
Ph	Me	***R***	**a**	85	93 (*R*)
Ph	Et	***R***	**b**	65	76 (*R*)
Et	Me	***R***	**c**	71	74 (*S*)
Bu	Me	***S***	**d**	80	81 (*R*)
i-Pr	Me	***R***	**e**	71	84 (*R*)
t-Bu	Me	***S***	**f**	66	83 (*S*)
TMS	Me	***S***	**g**	62	90 (*R*)
CH_2=CH	Me	***S***	**h**	64	61 (*S*)

[a] The **a** series was performed with both (−)-**1*R*** and (+)-**1*S***. The **a*S***, **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. [b] Product ee determined by conversion to the Alexakis esters[6] and analysis by ^{31}P NMR.

Table 2. . Propargylboration of R_LR_SCO with **2**



R_L	R_S	**1**	series	**9**[a] (%)	% ee[b] (abs config)[c]
Ph	Me	***S***	**a**	81	97 (*R*)[d]
Bu	Me	***S***	**b**	62	84 (*R*)
c-C_6H_9[e]	Me	***S***	**c**	67	91 (*R*)
p-$MeOC_6H_4$	Me	***R***	**d**	95	92 (*S*)
p-BrC_6H_4	Me	***S***	**e**	80	98 (*R*)
p-$O_2NC_6H_4$	Me	***S***	**f**	79	98 (*R*)
2-C_4H_3S[e]	Me	***S***	**g**	71	78 (*S*)
2-C_4H_3O[e]	Me	***S***	**h**	82	80 (*R*)
Ph	Et	***S***	**i**	63	64 (*R*)

[a] In each case, the crystalline byproduct **8** was recovered (50−85%) using a pseudoephedrine (PE) workup (i.e., (1*R*,2*R*)-(−)-PE for (+)-**8*S*** and (1*S*,2*S*)-(+)-PE for (−)-**8*R***). 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**. [b] Product ee was determined by reaction of **8** with phosphorus CDA and analysis by ^{31}P NMR. [c] Configuration predicted by analogy to **9a**. [d] Allenic alcohol **9a** was converted to the known 2-hydroxy-2-phenylpropionic acid and the sign of rotation was compared with the reported value. [e] 1-Cyclohexenyl, 2-thienyl, and 2-furyl.

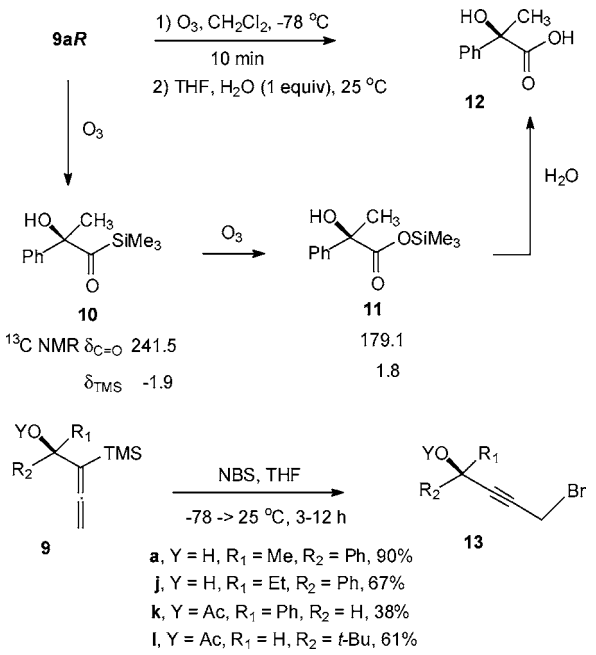
2). Reaction times for these substrates varied considerably from 3 to 36 h for the methyl ketones. The aryl ketones,

(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 °C. However, even highly demanding substrates, such as 2-hexanone, give **9** with high selectivity (i.e., **9b**, 84% ee).

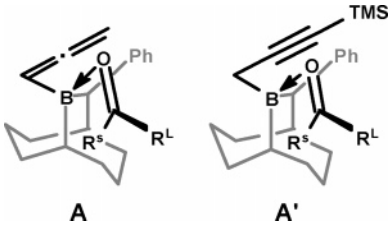
The absolute stereochemistry for **9a** was determined by its conversion to the known atrolactic acid (**12**) through simple ozonolysis (Scheme 2). This oxidation is greatly

Scheme 2



facilitated by the α-TMS substitution in **9**, which permits the ozonolysis to proceed directly to **11** through **10**.[1a] To discover other potential applications for this α-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[3b,c] in **2** which leads to **9**.

As previously described,[4] 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 **1*R*** and **2*R***, 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.



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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.

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