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Nonracemic α-Allenyl Carbinols from Asymmetric Propargylation with the 10-Trimethylsilyl-9-borabicyclo[3.3.2]decanes†

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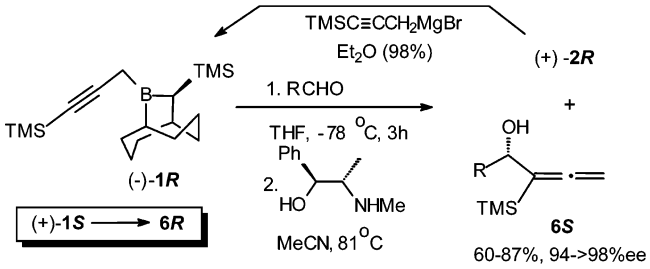
ABSTRACT



The asymmetric propargylboration of aldehydes at −78 °C in <3 h with 1 provides silylated α-allenyl carbinols 6 (60−87%) in high ee (94% to >98% ee). The reagents 1 are easily prepared in both enantiomeric forms with a simple Grignard procedure and air-stable borinate complexes 2. The ozonolysis of 6 proceeds smoothly through an acylsilane intermediate to give a TMS ester, which is hydrolyzed to the α-hydroxy acid quantitatively with water.

The asymmetric propargylboration of aldehydes provides a convenient route to nonracemic α-allenyl carbinols. The first successful asymmetric propargylboration was accomplished by Corey with 1,3,2-diazaborolanes prepared through Sn/B exchange and 1,3-transposition with allenyltributyltin.[1] These proved to be highly effective and enantioselective reagents for the asymmetric synthesis of these useful alcohols.[2]

The racemic version of propargylboration was first reported by Zweifel.[3] He clearly demonstrated the use of substitution to control propargyl- versus allenylboration under either kinetic or thermodynamic reaction conditions. This phenomenon was elegantly utilized by Wang, who took advantage of the steric bulk of the trimethylsilyl (TMS) group to prepare γ-silylated propargylboranes cleanly free of allenylic impurities.[4] This route to α-allenyl carbinols was later developed by Brown into a second effective asymmetric process using his diisopinocampheylborane reagents ($(Ipc)_2B$-$CH_2C{\equiv}CTMS$).[5] Moreover, the α-TMS group in the products can be easily removed to provide the parent α-allenyl carbinols. Compared to alternative routes,[6] the propargylboration process is unrivaled in convenience and selectivity. However, issues that could be addressed with new systems include (1) a more direct route to the reagents through simple Grignard procedures avoiding other organometallic intermediates, (2) the use of air-stable precursors to simplify the experimental operations, and (3) the inclusion of effective recovery procedures to recycle the chiral borane moiety. The

† This work is belatedly dedicated to Professor Elias J. Corey on the occasion of his 77th birthday.

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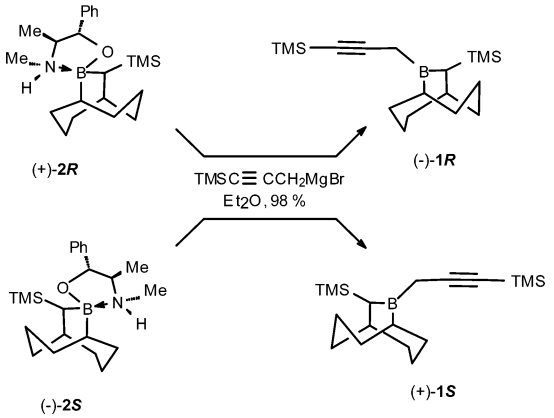
B-(γ-trimethylsilylpropargyl)-10-trimethylsilyl-9-borabicyclo-[3.3.2]decanes (**1**) were designed to meet these requirements.

Recently, we reported the simple two-step preparation of both enantiomeric forms of the air-stable crystalline pseudoephedrine (PE) complexes **2** in a combined overall yield of 63% from *B*-MeO-9-BBN.[7] These complexes served as efficient precursors to the corresponding allyl- and allenylboranes through simple Grignard procedures. In an analogous manner, the addition of the Grignard reagent derived from 3-bromo-1-TMS-1-propyne was found to proceed cleanly with either (+)-**2*R*** or (−)-**2*S*** to provide either (−)-**1*R*** or (+)-**1*S***, respectively (98%) (Scheme 1). The

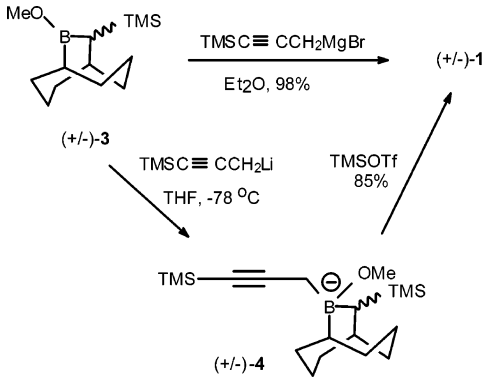
Scheme 1



pseudoephedrine was also recovered from its Mg salt byproduct in 92% yield.

For analytical purposes, it was necessary to prepare (±)-**1**, providing us with an opportunity to compare our Grignard approach to **1** to the previously reported route to propargylboranes through the lithiation of 1-TMS propyne with *t*-BuLi.[4,5a] First, the Grignard method was examined employing (±)-**3**, and it was found that the addition of TMSC≡CCH_2MgBr in ether followed by a slow warm-up to room temperature gives (±)-**1** cleanly (98%) (Scheme 2).

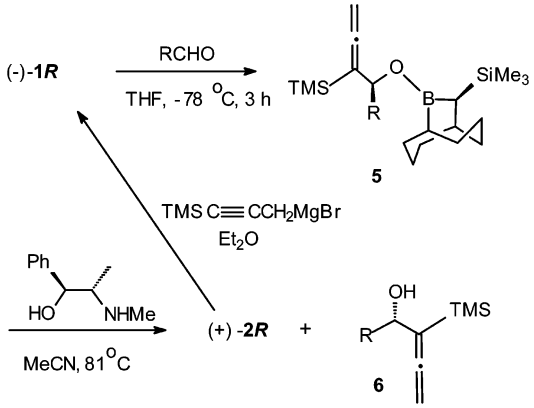
Scheme 2



No double addition was observed and no added Lewis acids were required to generate the reagent. By contrast, the corresponding lithium reagent adds cleanly to **3** at −78 °C to produce a stable methoxyborate complex (^{11}B NMR δ 6.8). However, the clean Lewis acid mediated demethoxylation of this complex proved to be difficult, with varying amounts of depropargylation being observed by ^{11}B NMR with added Lewis acids. Fortunately, TMSOTf solved the problem as it had in the related crotyl system, providing (±)-**1** in 85% yield. However, this method is further complicated by difficulties encountered in the removal of the LiOTf salt from **1**, which leads to lower product yields. We also used this method to prepare the optically pure isomers of **1** from either (−)-**3*R*** or (+)-**3*S***. Since these precursors are prepared from **2**, the Grignard route to **1** is far superior to the lithiation protocol.

With efficient routes to both enantiomeric forms of **1** in hand, the propargylboration of representative aldehydes was examined at −78 °C (3 h) to provide both the corresponding silylated α-allenyl carbinols **6** (60−87%) and the recovered crystalline **2** (70−85%) efficiently (Table 1). The propar-

Table 1. Asymmetric Propargylboration of RCHO with **1**



R in RCHO	**1**	**6**	yield (%)[a]	[α]$^{25}_D$ (abs config)	% ee[b]	**2**
Me	*R*	a	71	−9.0 (*S*)	94	78
Pr	*S*	b	87	−6.0 (*R*)	98	85
i-Pr	*S*	c	77	−5.4 (*R*)	97	78
t-Bu	*S*	d	80	+5.0 (*R*)	98	70
Ph	*R*	e	60	+129.0 (*S*)	98	70
(*E*)-MeCH=CH	*R*	f	87	+58.7 (*S*)	97	85

[a] Isolated yield of analytically pure material. [b] Determined by comparison of the ^{1}H and/or ^{13}C NMR peak areas for diastereomeric pairs of the corresponding Mosher esters.

gylborane **1** is directly regenerated from **2** through the simple Grignard procedure (98%). The six representative substrates examined include aliphatic (primary, secondary, and tertiary), aromatic, and α,β-unsaturated aldehydes. In each case, the intermediate borinic esters **5** were formed cleanly (^{11}B NMR δ ∼54). Treatment with PE converts these intermediates to **2**, which crystallizes from MeCN, facilitating the simple distillative isolation of **6** (60−87%). The optical purities of

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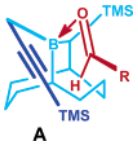
6 were conveniently accessed through the NMR analysis of their corresponding Mosher esters. The process is highly enantioselective, providing **6** in high optical purity (94% to >98% ee).

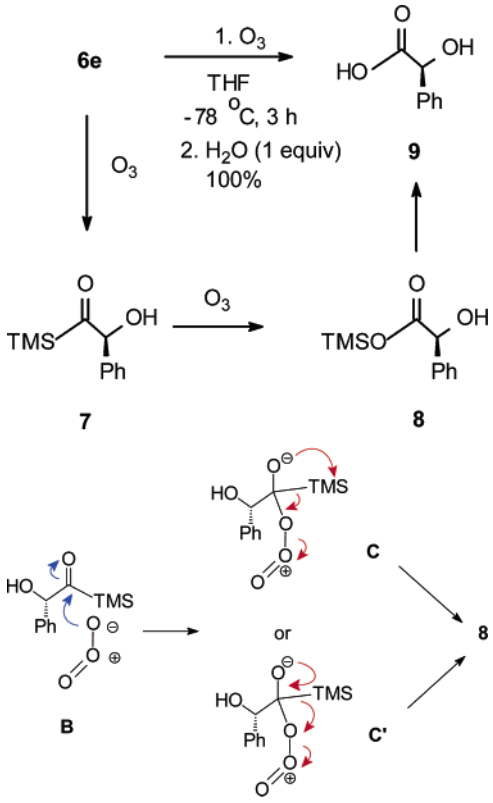
The absolute stereochemistry of **6** was assigned on the basis of values reported by Brown.[5a] These assignments are also wholly consistent with those resulting from allyl-, crotyl-, and allenylboration with the 9-borabicyclo[3.3.2]-decane (BBD) reagents. The most energetically favorable pre-transition state complex **A** for propargylation with **1** leads to the correct prediction for the product stereochemistry in each of the cases examined (i.e., **1*R*** → **6*S***, **1*S*** → **6*R***).



A

To confirm these assignments for **6**, we noted that Corey had previously demonstrated that α-allenyl carbinols provide ready access to α-hydroxy aldehydes though an ozonolysis protocol.[2f] These aldehydes were converted to the corresponding carboxylic acids with excess sodium chlorite (10 molar equiv). Clearly, the TMS group in the propargyl moiety plays a critical role in providing isomerically pure **1**, which in turn results in α-allenyl carbinols with *β*-TMS substitution. Protiodesilylation can be achieved,[5a] but a more constructive use for this TMS group was envisaged, namely, through its potential to facilitate the conversion of **6** to α-hydroxy acids through ozonolysis without hydroxyl protection or aldehydic oxidation.[2f] We selected the conversion of **6e** to the known mandelic acid (**9**) through a silyl-modified version of the ozonolysis protocol. In this process, the ozonolysis of **6e** leads to the intermediate acylsilane **7** (^{13}C NMR *δ* 241.5 (SiC═O), −2.8 (TMS)), which is further directly oxidized with ozone to the corresponding silyl ester **8** (^{13}C NMR *δ* 176 (SiOC═O), 1.8 (TMS)). Silyl ester **8** is hydrolyzed with the addition of water (1.0 equiv) to provide **9** quantitatively (Scheme 3). Although aldehydes can be oxidized by ozone under strongly basic conditions in alcohol solution,[8] the present process appears to be very different. To our knowledge, this ozone-mediated acylsilane oxidation is unknown. However, this functionality is known to be highly susceptible to mechanistically related oxidants[9] and its survival under oxidative conditions can be quite challenging.[10] At present, we view this oxidation as occurring through a nucleophilic process (**B**) followed by either a 1,2-migration of silicon from carbon to oxygen either directly (**C′**) or through a Brook-type rearrangement (**C**) (Scheme 3). Clearly more studies are needed to better understand this intriguing process.

Scheme 3



In summary, the reagents **1** are easily prepared from the air-stable crystalline borinic esters complexes **2** through a simple Grignard procedure. Alternatively, they also are available from the previously known lithiation protocol that has been successful for other dialkylborane systems.[4,5] Isolable, **1** undergoes clean addition to even hindered aldehydes in <3 h at −78 °C. In the asymmetric propargylboration process, the reagents **1** are used with a nonoxidative workup that provides the recovered chiral borane moiety in the form of the air-stable and recyclable complex **2** (70−85%). This is directly converted back to **1**. The pseudoephedrine is also recycled so that the BBD reagents effectively act as surrogates for this asymmetric process. Either enantiomeric form of the silylated α-allenyl carbinols **6** is obtained in good to excellent yields (60−87%) in high ee (94% to >98%). The TMS substitution in **6** facilitates the remarkably clean conversion of **6** to the corresponding α-hydroxy carboxylic acids directly through ozonolysis. This process takes full advantage of the new ozone-mediated oxidation of acylsilanes to silyl esters. The new reagents **1** provide attractive alternatives to existing reagents for the asymmetric synthesis of the highly versatile α-allenyl carbinols.

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Supporting Information Available: Full experimental procedures and spectra for **1** and **6**−**9** and derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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