J|A|C|S
ARTICLES
Published on Web 05/10/2005

Asymmetric Allyl- and Crotylboration with the Robust, Versatile, and Recyclable 10-TMS-9-borabicyclo[3.3.2]decanes

Carlos H. Burgos,† Eda Canales, Karl Matos,‡ and John A. Soderquist*

Contribution from the Department of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931-3346

Received October 20, 2004; E-mail: jas@janice.uprr.pr

Abstract: The remarkable versatility and selectivity of the 10-(trimethylsilyl)-9-borabicyclo[3.3.2]decanes (10-TMS-9-BBDs) in the allyl- and crotylboration of representative aldehydes are reported. The new reagents are prepared through air-stable crystalline pseudoephedrine borinic ester complexes of the 10-TMS-9-BBDs (**4**), which are available in 63% overall yield from *B*-MeO-9-BBN through a simple two-step procedure. These complexes **4** are directly converted to the corresponding *B*-allyl-10-TMS-9-BBDs (**1**) with allylmagnesium bromide, which either can be isolated (98%) or used in situ for the allylations. The remarkable enantioselectivity (96 to ≥99% ee) of these reagents in the rapid (<3 h), asymmetric allylboration process at −78 °C is only slightly diminished when it is conducted at 25 °C, a phenomenon attributable to its rigid bicyclic structure. In addition to providing the homoallylic alcohols **6** efficiently (68−80%), the procedure also permits the efficient recovery of **4** (68−84%) for the direct regeneration of **1**. Alternatively, an oxidative workup procedure can be used for the preparation of **6**. The reagent gives predictable stereochemistry and exhibits an extremely high level of reagent control in the allylboration of D-glyceraldehyde acetonide. A simple and efficient procedure has been developed for the preparation of all four geometric and enantiomeric isomers of the *B*-crotyl-10-TMS-9-BBDs (**10**) from optically pure enantiomers of *B*-MeO-10-TMS-9-BBD (**3**). These reagents **10** also add rapidly (<3 h) and efficiently to representative aldehydes at −78 °C, providing ready access to all four of the possible stereoisomers of the β-methyl homoallylic alcohols **12**−**15** (69−92%) in high dr (≥98:2) and ee (94−99%).

Introduction

The preparation of nonracemic homoallylic alcohols through the asymmetric allylboration of aldehydes represents an extremely important process and one that has undergone continuous evolution since its discovery by Hoffmann over 2 decades ago.[1] Alternatives to allylboration including catalytic processes have also been reported.[2] It has been pointed out that an ideal reagent for the asymmetric allylation of aldehydes should be (1) easily prepared in both enantiomeric forms, (2) a stable reagent that can be prepared and stored in bulk and utilized through trivial procedures, (3) user and environmentally friendly, and (4) generally effective, exhibiting high efficiency and enantioselectivity.[2a] Other attractive features for this ideal system would be that it is (5) easily recycled, (6) relatively insensitive to the reaction temperature, (7) highly selective with chiral substrates, and (8) easily modified to provide ready access to more complex allylic systems such as the corresponding crotylboranes. In this paper, we describe the preparation of the remarkably robust 10-trimethylsilyl-9-borabicyclo[3.3.2]decanes (10-TMS-9-BBDs) and their use in the asymmetric allyl- and crotylboration of representative aldehydes, demonstrating that this new stable chiral ligation for boron largely meets all of these criteria.

Asymmetric allylboration is generally viewed as occurring via a chairlike transition state, with allyldialkylboranes being significantly more reactive than their boronic ester and related counterparts.[1,3] The reactivity of the latter can be increased through the incorporation of electron-withdrawing groups into the ligands of these esters or by added Lewis acid catalysts, and this generally results in enhanced selectivities. Moreover, the valuable diol precursors to these reagents can also often be recovered.[1d,4] However, the chiral dialkylborane derivatives do

† Current address: Merck, Sharp & Dohme Quimica de Puerto Rico, Inc., Barceloneta, PR 00617-6060.

‡ Current address: BASF Corp., Inorganics, Evans City, PA 16033.

(1) (a) Herold, T.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 768. (b) Herold, T.; Schrott, C.; Hoffmann, R. W. *Chem. Ber.* **1981**, *114*, 359. (c) Hoffmann, R. W.; Herold, T. *Chem. Ber.* **1981**, *114*, 375. See also: (d) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23 and ref. cited therein. (e) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701. (f) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644. (g) Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 3838. (h) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308. (i) Morgan, J. B.; Morken, J. P. *Org. Lett.* **2003**, *5*, 2573. (j) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375. (k) Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508.

(2) (a) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Waltz, K.; Gavenonis, J.; Walsh, P. J. L. *Angew. Chem., Int. Ed.* **2001**, *41*, 3697. (d) Kennedy, J. W. J.; Hall, D. G *J. Org. Chem.* **2004**, *69*, 4412. (e) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (f) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (g) Kim, J. G.; Waltz, K. M.; Garcia, I. F.; Kwiatkowski, D.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 12580. (h) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593.

(3) (a) Yamamoto, Y.; Asoa, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692. (c) Li, Y.; Houk, K. *J. Am. Chem. Soc.* **1989**, *111*, 1236.

(4) (a) Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806.

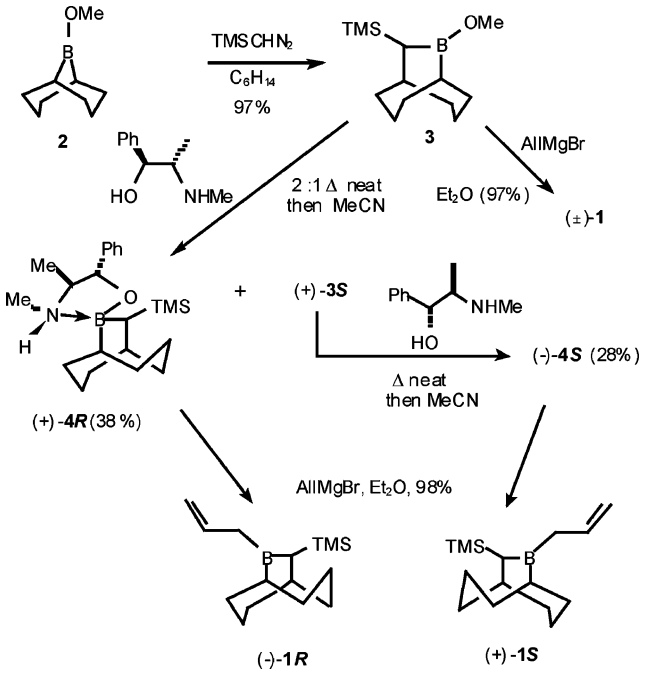
10.1021/ja043612i CCC: $30.25

have inherent advantages over their boronate counterparts. The lack of heteroatom spacers permits the chirality to be placed closer to the boron center, which also generally results in increased selectivity. Also, the fact that B−C bonds are hydrolytically stable has permitted nonoxidative workup procedures to be devised for the diterpenylboranes processes, which enable the chiral boron moiety to be recycled. Unfortunately, these reagents must be freshly prepared from high-purity air-sensitive precursors prior to their use in the allylboration process.[1d,5a] Moreover, with the selectivities of reagents such as allyldiisopinocampheylborane (Ipc_2BAll) exhibiting significant temperature dependence, their reactions are best conducted at −100 °C under salt-free conditions.[5b]

A powerful extension of the allylboration process, namely, asymmetric crotylboration,[6] represents one of the most useful organoborane conversions. Providing highly versatile nonracemic stereodefined β-methyl homoallylic alcohols, the process simultaneously produces two contiguous stereogenic centers in a controlled and predictable manner. After the pioneering work of Hoffmann,[6] effective tartrate-[7] and terpene-based[8] reagents have expanded the scope, versatility, and selectivity of the process.[9] Chiral organoborane catalysts were also introduced by Yamamoto, which allowed achiral crotylsilanes and stannanes to provide effective crotyl sources for the process.[10] Recently, Lewis acids have been demonstrated to markedly enhance the rate of crotylboration.[11] While chiral Lewis acids do provide some enantioselectivity with achiral crotylboranes,[2e] the enhanced reactivity of chiral boronic esters with added $Sc(OTf)_3$ provides highly enantioselective crotylborations.[11b] Related silane combinations are also useful for asymmetric crotylation,[2b,12] as are chiral crotylsilanes which have been developed for the uncatalyzed crotylation of aldehydes.[13] These advances notwithstanding, asymmetric crotylboration is particularly versatile, finding numerous applications for which the syntheses of superstolide A and B, tetronasin, venturicidines, swinholide A, and, most recently, (−)-dictyostatin are representative.[14]

A variety of methods can be used for the synthesis of stereodefined γ-substituted allylboranes.[1d,2d] However, the parent crotyl systems are generally best prepared in a highly stereoselective manner through the addition of the appropriate Schlosser "crotylpotassium" reagents to organoborane substrates.[4,7−9] As with allylboration, these reagents add to aldehydes in a highly diastereoselective manner, presumably also through a chairlike transition state, faithfully transmitting the borane geometry into the product alcohols. Thus, (*Z*)- and (*E*)-boranes produce *syn*- and *anti*-β-methyl homoallylic alcohols, respectively.[3] Chiral reagents have been derived from terpenes,[8] tartrates,[7] tartramides,[1g] and borolanes,[9] which exhibit enantioselectivities far exceeding those of asymmetric catalytic processes employing stoichiometric quantities of achiral crotylboranes.[2e] The robust 10-TMS-9-BBD ring system appeared to us to have the potential to provide very reactive and selective reagents. Further, we felt that they would be as easy to prepare and recycle as Brown's terpene-derived reagents,[8] but closer to Roush's tartrates and tartramides[1f,g,7] in terms of ease of handling, purification, storage, and use.

Scheme 1



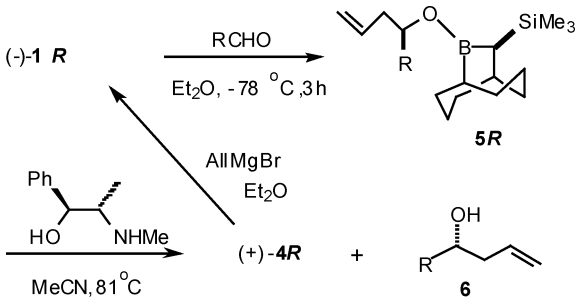
Results and Discussion

Synthesis of the Allylboranes 1. Recently, we discovered that the stable, commercially available $TMSCHN_2$ undergoes the clean insertion of CHTMS into a ring B−C bond in *B*-R-9-BBNs.[15] Fortunately, this process (10 h, C_6H_{14}, 70 °C) is also successful for **2**, affording the very stable *B*-MeO-10-TMS-9-BBD (**3**) in 97% yield after distillation (bp 80 °C, 0.10 mmHg) (Scheme 1). Moreover, **3** is stable to the open atmosphere for brief periods of time (17 h, 3% oxidation), in marked contrast to **2** and other borinate esters such as $MeOB(Ipc)_2$. Moreover, **3** is readily converted to (±)-**1** with allylmagnesium bromide (AllMgBr) in ether (98%).

Employing a modified version of the Masamune resolution protocol,[16] (±)-**3** was added to 0.5 equiv of (1*S*,2*S*)-pseudoephe-

(5) (a) Brown, H. C.; Racherla, U. S.; Liao Y.; Khanna, V. V. *J. Org. Chem.* **1992**, *57*, 6608. (b) Racherla, U.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614.
(6) See, for example: (a) Hoffmann, R. W.; Ladner, W.; Steinbach, K.; Massa, W.; Schmidt, R.; Snatzke, G. *Chem. Ber.* **1981**, *114*, 2786. (b) Hoffmann, R. W.; Zeiss, H.-J.; Ladner, W.; Tabche, S. *Chem. Ber.* **1982**, *115*, 2357. (c) Hoffmann, R. W.; Endesfelder, A.; Zeiss, H.-J. *Carbohydr. Res.* **1983**, 320.
(7) (a) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339. (c) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. (d) Roush, W. R.; Ando, K.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *Tetrahedron Lett.* **1988**, *44*, 5579.
(8) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (b) Brown, H. C.; Racherla, U. S.; Liao, Y.; Khanna, V. V. *J. Org. Chem.* **1992**, *57*, 6608. (c) Brown, H. C.; Bhat, K. S.; Randad, R. *J. Org. Chem.* **1987**, *52*, 3701.
(9) For chiral borolanes, see: Garcia, J.; Kim, B.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831.
(10) (a) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett.* **1991**, 561. (b) Marshall, J. A.; Tang, Y. *Synlett.* **1992**, 653.
(11) (a) Kennedy, J. W.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160.
(12) (a) Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, *122*, 12806. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. See also: (c) Schaus, J. V.; Jain, N.; Panek, J. S. *Tetrahedron* **2000**, *56*, 10263.
(13) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375.
(14) (a) Yu, W.; Zhang, Y.; Jin, Z. *Org. Lett.* **2001**, *3*, 1447. (b) Ley, S. V.; Clase, J. A.; Mansfield, D. J.; Osbor, H. M. I. *J. Heterocycles Chem.* **1996**, *33*, 1533. (c) Hoffmann, R. W.; Rolle, U.; Gottlich, R. *Liebgs Ann.* **1996**, 1717. (d) Paterson, I.; Yeung, K.-S.; Ward, R. I.; Cumming, J. G.; Smith, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 9391. (e) Patron, A. P.; Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1147. (f) Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Patron, A. P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1151. (g) Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629.

Scheme 2



drine (PE) in MeCN, which gave a 38% yield of (+)-**4*R*** as a pure crystalline compound, leaving (−)-**3*R*** in solution. After concentration of the supernatant to remove the liberated MeOH, 0.5 equiv of (1*R*,2*R*)-PE was added to a fresh solution of the residue in acetonitrile, ultimately giving a 28% yield of the pure crystalline (−)-**4*S***. Reversing this order gives first, (−)-**4*S*** and, second, (+)-**4*R***, also in a 66% combined total yield of enantiomerically pure forms of **4** from (±)-**3**! These complexes are air-stable and can be stored indefinitely. The complex (+)-**4*R*** is wholly chelated in the solid state,[15] while, in solution, **4** exists in both the open and closed forms (^{11}B NMR (C_6D_6) δ 56.3, 23.7).

The direct conversion of **4** to **1** was accomplished with AllMgBr in Et_2O, the metathesis proceeding very cleanly at −78 °C. The stable allylboranes **1** can be isolated (98%) in chemically and optically pure form through simple filtration through Celite under N_2 to remove the Mg^{2+} salts followed by concentration in vacuo. Under N_2, **1** is stable for weeks at 25 °C. *In practice, **1** need not be isolated, but rather merely quantitatively generated with the simple addition of AllMgBr in Et_2O to **4**.* This admixture is directly used for the allylations, the Mg^{2+} salts not interfering with the rate of allylation, in contrast to the behavior of terpenyl reagents.[5b] The ease and efficiency of the preparation of both enantiomers of **1** from **2** in 63% overall yield is greatly enhanced by the air-stability of its precursor, **4**, which largely avoids many of the difficulties usually associated with dialkylborane reagents.

Asymmetric Allylboration with 1. The asymmetric allylboration of representative aldehydes was conducted with either (−)-**1*R*** or (+)-**1*S*** in Et_2O (3 h, −78 °C), with the homoallylic alcohols **6** being isolated in high ee (96 to ≥99% ee) (Scheme 2, Table 1). This process is quite general, being effective for alkyl, aryl, heteroaryl, and unsaturated aldehydes. The optical yields of **6** were determined by the ^{1}H and ^{13}C NMR and/or GC analysis of the known Mosher esters of these alcohols.[17] In each case, the racemic alcohols (±)-**6** were also prepared through the addition of AllMgBr or (±)-**1** to the starting aldehydes. Using synthetic mixtures, we established our limit of detection as 1%, except for **6b**, **6c**, and **6e**, where 0.5% of the diastereomeric Mosher esters could be observed. Comparing these results to other known reagents reveals that **1** equals or exceeds the selectivity observed for any alternative process at −78 °C.[1,2,4,7−10,17]

Table 1. Allylboration of RCHO with **1**

R in RCHO	**1**	series	**6** (%)[a]	% ee[b] (abs config)
Me	R	a	71	96 (*S*)
Pr	R	b	79	≥99 (*S*)[d]
i-Pr	S	c	70	≥99 (*S*)[c]
t-Bu	R	d	79	≥98 (*R*)[c]
CH_2=CH	S	e	71	≥99 (*S*)[c,e]
Ph	S	f	80	≥98 (*S*)[c,e]
4-$MeOC_6H_4$	R	g	90	96 (*R*)[c]
4-$O_2NC_6H_4$	R	h	87	97 (*R*)[c]
2-furyl	R	i	86	97 (*R*)[c]
t-PhCH=CH	R	j	92	97 (*R*)[c]

[a] All runs were made in duplicate (at least) and those of the **a** and **f** series were performed with both (−)-**1*R*** and (+)-**1*S***. For the **a**−**f** series, the intermediate **5** was isolated (87−100%) and converted to **6** and recovered **4** (68−84%) via the PE workup procedure. For the **g**−**j** examples, an oxidative workup procedure was used. [b] Product ee determined by conversion to the Mosher esters and analysis by ^{13}C NMR, ^{1}H NMR and ^{13}C NMR, or GC as noted. [c] ^{13}C NMR. [d] ^{1}H NMR and ^{13}C NMR. [e] GC.

As part of the standard protocol, the borinic ester intermediates **5** were isolated in excellent yields in essentially pure form following removal of the solvent (Table 1, series **a**−**f**). For the reactions of (−)-**1*R***, solutions (~0.5 M) of **5*R*** and (1*S*,2*S*)-PE (1.0 equiv) in MeCN were heated at reflux temperature to effect the transesterification, giving **6** together with crystalline (+)-**4*R***, which is easily isolated (70−80%) by simple filtration. An analogous procedure was used for the (+)-**1*S*** reactions employing (1*R*,2*S*)-PE to provide **6** and crystalline (−)-**4*S***. The homoallylic alcohols **6** were isolated by simple distillation (67−84%). The byproduct **4** was recycled through its direct conversion back to **1** though a simple Grignard procedure, avoiding the extra steps needed to recycle other reagents.[1,4,5a] Alternatively, an oxidative workup procedure can be employed in the allylation process (Table 1, series **g**−**j**).

In the absence of high-level computational data, MM calculations[18] provide useful models for the prediction of the product stereochemistry through the relative stabilities of their diastereomeric pre-transition state complexes.[19] These calculations reveal that the *B*-chiral *anti*-aldehyde complex which forms cis to the 10-TMS group (i.e., **7**) is favored (~3 kcal/mol, R = Ph) over any conformation of its syn and/or trans counterparts leading to the selective allylation of the *re* face of RCHO with the **1*R*** reagent. In **7**, the γ-allylic carbon is within 3.0 Å of the aldehydic carbon, well positioned for collapse to the expected chairlike transition state. Any attempt to reach an alternative transition state through rotation about the B−O and B-allyl bonds is thwarted by the TMS group, which blocks this pathway.

7

(15) Soderquist, J. A.; Matos, K.; Burgos, C. H.; Lai, C.; Vaquer, J.; Medina, J. R.; Huang, S. D. In *ACS Symposium Series 783*; Ramachandran, P. V., Brown, H. C., Eds.; American Chemical Society: Washington, DC, 2000; Chapter 13, p 176.
(16) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892.
(17) (a) Brown, H. C.; Ramachandran, P. V. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Greenwich, CT, 1995; Vol. 1, p 147. (b) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (c) Brown, H. C.; Jadhav, P. K. *J. Org. Chem.* **1984**, *49*, 4089. (d) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **1986**, *51*, 432. (e) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. (f) Soai, K.; Ishizaki, M.; Yokoyama, S. *Chem. Lett.* **1987**, 341. (g) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701.
(18) Performed using the Spartan 4.0.4a GL MM program.
(19) Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1998**, *63*, 8331.

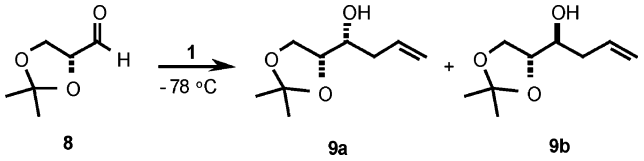
Table 2. Temperature Effects: **1** vs Ipc_2BAll

	1*R* (% ee)[a]		Ipc_2BAll (% ee)[b]
temp (°C)	PhCHO	MeCHO	MeCHO
25	90	94	NA
0	93[c]	93	79
−25	94	98	85
−78	>98 (94[d])	96	93

[a] Analysis of Mosher esters by ^{13}C NMR. [b] Data from ref 20. [c] For (+)-**1*S***. [d] For Ipc_2BAll.

The selectivity of **1** exhibits little temperature dependence in contrast to reagents such as Ipc_2BAll (Table 2).[20] We attribute this to the rigid bicyclic ring system in **1**, the chiral integrity of which is largely maintained despite increasingly populated higher rotational states. As can also be envisaged through **7**, the chiral pocket for **1** is too small to easily accommodate inward groups larger than H. Thus, the allylboration of ketones is much slower and less selective than for aldehydes (e.g., PhCOMe, 2 d, 25 °C, 85%, 62% ee).

The presence of a proximate stereogenic center in RCHO can markedly influence the diastereoselectivity of the allylboration. For **1**, we examined its selectivity for D-glyceraldehyde acetonide (**8**, 99% ee), an extensively studied substrate.[4] Its

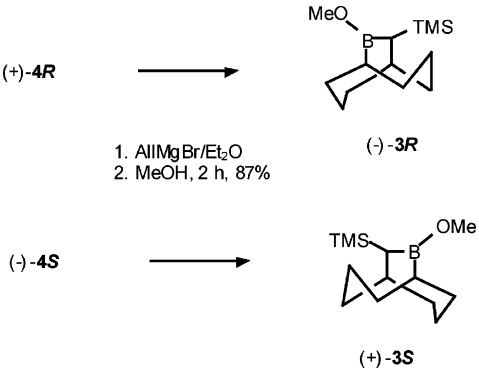


reaction with (−)-**1*R*** gave a >99:1 mixture of the (2*R*,3*R*)-threo (**a**) and (2*R*,3*S*)-erythro (**b**) diastereomers of **9**, whereas (+)-**1*S*** gave these products in a 5:95 dr.[21] These selectivities for **1** are comparable to the best tartramide reagents for this substrate.[4]

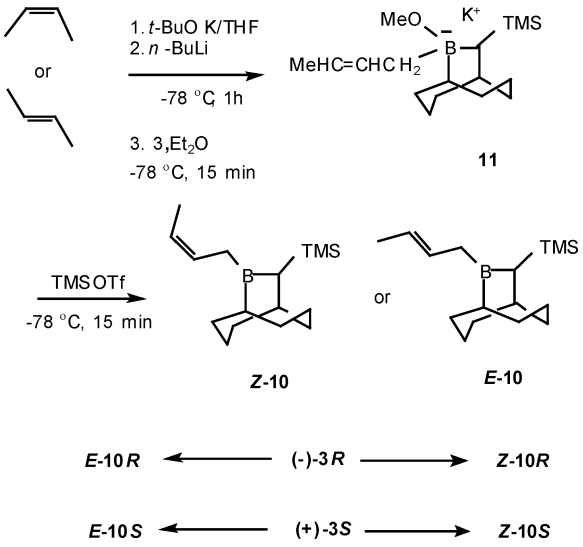
Synthesis of the Crotylboranes 10. With the general versatility and remarkable selectivities exhibited for **1** in the asymmetric allylboration process, we chose to extend this general reaction protocol to crotylboration. Unfortunately, all attempts to find a clean and effective procedure for the direct conversion of the complexes **4** to the crotyl reagents **10** were unsuccessful. Only reagents of the general type RMgBr appear to be amendable to this method, and Grignard procedures give crotylborane mixtures.[22] On the basis of other dialkyl systems, **3** provides the logical precursor to **10** through the standard protocol using the Schlosser reagents.[23] As noted above, **3** is a very "user friendly" borinic ester, being distillable, storable, and unusually resistant toward air oxidation. These characteristics of **3** were expected to significantly reduce the complexity of the operations required in generating **10**.

We considered several potential routes to the optically pure forms of **3**, finding that the simplest and most efficient method was through the generation of the allylboranes **1** from either (+)-**4*R*** or (−)-**4*S*** and their methanolysis (2 h, reflux) to provide, after distillation, pure (−)-**3*R*** and (+)-**3*S***, respectively, both in

Scheme 3



Scheme 4



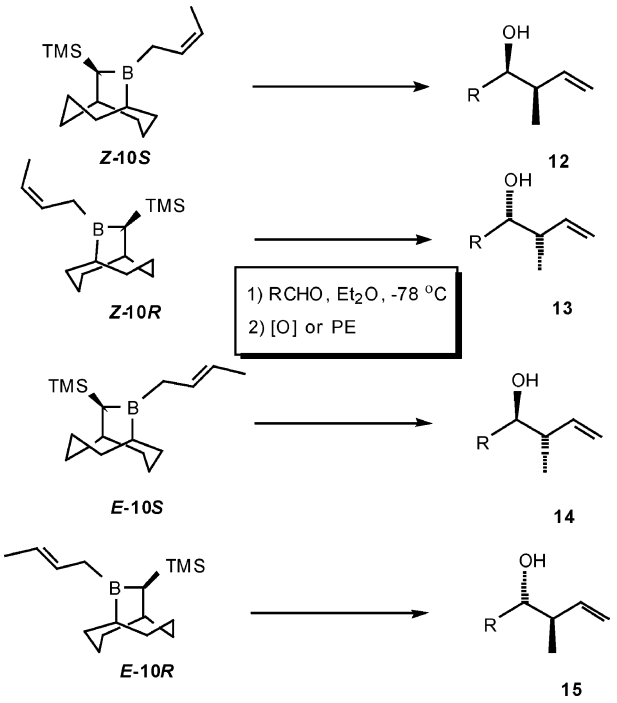
87% yield (Scheme 3). Because no significant manipulation of **1** is required in the procedure and its methanolysis is very clean, producing only propene as a byproduct, the operation is exceedingly simple, with **3** being easy to isolate, handle, and store.

By analogy to Brown's preparation of his terpene-derived crotylboranes,[8] the **3** → **10** conversion was examined with (±)-**3** employing Schlosser's "Superbase" to selectively generate the crotylmetallic species from either *cis*- or *trans*-2-butene, followed by their addition to **3** giving the borinate complexes **11**, which are demethoxylated with a Lewis acid to give the crotylborane **10**.[8] Our modifications include (1) the use of THF solutions of KO(Bu-*t*) rather than the solid reagent, which dramatically reduces the time required for the deprotonation of *cis*-2-butene from 12 → 1 h and increases the geometric purity of *E*-**10** from 94 to 98%; (2) conducting the entire process at −78 °C, which results in the clean formation of **11** (^{11}B NMR δ 3.6), avoiding isomerization of the "crotylpotassium" reagents and the double addition of the crotylmetallic (^{11}B NMR δ −9.6) to **3**; and (3) the use of TMSOTf as the Lewis acid, which avoids the unwanted decrotylation of **11** to regenerate **3** [e.g., BF_3−Et_2O or $MgBr_2$ (40%), TMSCl (20%)] and cleanly produces **10** (95%) in high geometric purity (≥98%). With these modifications in place, both *Z* and *E* isomers of **10** in either enantiomeric form as well as, importantly, also in racemic form, are readily prepared from **3** (Scheme 4).

With efficient procedures for all of the isomers of **10** in hand, we chose to examine their configurational stabilities, since

(20) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1996**, *51*, 432.
(21) The ^{13}C NMR signals for the C-4 position in **9a** and **9b** were cleanly resolved, appearing at δ 38.5 and 37.6, respectively (δ 35.1 and 35.6 in their Mosher esters).
(22) Hoffmann, R. W.; Niels, G.; Schlapback, A. *Pure Appl. Chem*. **1990**, *62*, 1993.
(23) Fujita, L.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258.

Scheme 5



crotylboranes are prone to isomerization through 1-methallylboranes via 1,3-boratropic rearrangements.[8a] This process is normally faster for BR_2 vs $B(OR')_2$ derivatives. Samples of both ***Z*-10** and ***E*-10** were examined by NMR after 1 week at 25 °C in $CDCl_3$ solution. The *E* isomer, which was initially 98:2 *E/Z*, was isomerized to 84:16 during this period. The *Z* isomer (≤2:98 *E/Z*) was more affected, giving a 53:47 *E/Z* mixture. As a consequence, the reagents **10** were not stored but rather generated as needed for the crotylboration process. The high reactivity of these trialkylboranes facilitates their clean addition to even highly hindered aldehydes in <3 h at −78 °C with no accompanying loss of the reagent's geometric purity.[24]

Asymmetric Crotylboration with 10. The crotylboration of representative aldehydes with ***Z*-10*S***, ***E*-10*S***, ***Z*-10*R***, or ***E*-10*R*** as well as with the racemic crotylboranes ***Z*-10** and ***E*-10** (for analytical purposes) was examined in detail (Et_2O, 3 h, −78 °C) (Scheme 5). The products β-methyl homoallylic alcohols **12**−**15** were isolated in good to excellent yields (68−94%) with high diastereoselectivity (dr >98:2) and enantioselectivity (94−99% ee) (Table 3). Through the choice of the appropriate crotylborane **10**, any and all of the stereoisomers of the β-methyl homoallylic alcohols can be prepared.

Three procedures were developed for the crotylboration process, all of which gave similar product yields and selectivities. Method A was developed to demonstrate that **10** is isolable and that its solutions can be used for the process. A standard oxidative workup (3 M NaOH, 30% H_2O_2) was employed. Method B uses the same workup but without isolation of the reagents **10**. Method C employs a solution of **10** followed by a nonoxidative workup through the addition of the appropriate

Table 3. Asymmetric Crotylboration of RCHO with **10**

R in RCHO	**10**	product	method[a]	yield (%)[b]	dr[c] syn/anti	ee[d]
Ph	***Z*-*S***	**12a**	A	72	≥98:2	98
Ph	***E*-*S***	**14a**	B	82	≤2:98	97
Me	***Z*-*S***	**12b**	C	68	≥98:2	95
Me	***Z*-*R***	**13b**	C	68	≥98:2	95
Me	***E*-*S***	**14b**	C	73	≤2:98	97
Pr	***Z*-*R***	**13c**	A	91	≥98:2	94
Pr	***E*-*R***	**15c**	A	94	≤2:98	96
t-Bu	***Z*-*S***	**12d**	B	92	≥98:2	94
t-Bu	***E*-*R***	**15d**	C	69	≤2:98	99

[a] Method A: isolated **10**, oxidative workup. Method B: in situ use of **10**. Method C: isolated **10**, pseudoephedrine workup. [b] Isolated yield. [c] Determined by comparison of peak areas for diastereomeric pairs of the alcohols through both ^1H and ^{13}C NMR. This was also checked through ^{13}C NMR of the corresponding Mosher esters. [d] Determined by comparison of the observed peak areas for several sets of signals derived from the diastereomeric pairs in the corresponding *R*-Mosher esters through both ^1H and ^{13}C NMR. For R = *t*-Bu, chiral diazaphospholidine derivatives were prepared and these were analyzed through ^{31}P NMR.

enantiomeric form of pseudoephedrine. This permits the efficient recovery of the chiral boron moiety **4** in 70−80% yield for recycling purposes.[25]

The syn and anti diastereomers of alcohols **12**−**15** give distinctly different ^{13}C NMR spectra, which were in complete agreement with those reported.[7b] In each case we determined the dr to be ≥98:2 for the major diastereomer produced, a direct reflection of the high geometric purities of **10** prepared through the Schlosser reagents. The enantiomeric excess for each β-methyl homoallylic alcohol **12**−**15** was normally determined from the ^1H and ^{13}C NMR analysis of the corresponding Mosher ester derivatives.[26] However, for the R = *t*-Bu examples (**12d**, **15d**), the product ee's were determined using chiral diazaphospholidine derivatives and ^{31}P NMR analysis.[27] The selectivities observed for **10** generally equal or exceed those of previously existing reagents. Data from the analogous asymmetric allylboration (vide ultra) and allenylboration[28] processes with our BBD system, together with the specific rotations for the R = Me (**b**) series, were used to assign the absolute stereochemistry of **12**−**15**.

As in the allylboration process with **1**, MM calculations[18] 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 which forms cis to the 10-TMS group (i.e., ***Z*-16**) is favored (~3 kcal/mol, R = Ph)

***Z*-16**

over any conformation of its syn and/or trans counterparts, leading to the selective allylation of the *re* face of RCHO with the ***10R*** reagent. Calculations with ***E*-16** produce similar results.

(24) The crotylborane geometry is faithfully reflected in the product alcohols (Table 3). While this is not new, the crotylboration with **10** is much faster than its isomerization, regardless of the reaction temperature. For example, early in the present studies we observed that ***E*-10** produced the β-methyl homoallylic alcohols in a 94:6 anti:syn ratio, both at at 25 and −78 °C. This led us to isolate ***E*-10** and determine its 94:6 *E/Z* ratio, ultimately optimizing this to ≥98:2 with our modified protocol.

(25) For a similar process with terpene-derived reagents, see ref 8b.
(26) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(27) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224.
(28) Lai, C.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 799.

Conclusions

In summary, through the insertion of CH(TMS) with trimethylsilyldiazomethane into a ring B−C bond in **2**, the remarkably stable chiral borinic ester **3** is prepared in pure form (97%). Both enantiomeric forms of the air-stable pseudoephedrine complexes **4** are isolable as pure crystalline compounds from **3** in 66% total overall yield. Reaction of AllMgBr and either enantiomer of **4** produces the allylborane **1**, which exhibits highly reagent controlled and enantioselective additions to representative aldehydes (<3 h at −78 °C). However, the allylations with **1** can also be conducted even at room temperature with only a moderate diminution of this exceptional enantioselectivity. The reagents **1** can either be isolated or used in situ with no interference from the byproduct magnesium salts being observed. A nonoxidative workup provides the efficient recovery of **4** for the regeneration of **1** (68−84%). The product homoallylic alcohols are isolated (68−80%) in high ee (96 to >99%). The allylborane **1** also serves as a useful intermediate for the synthesis of the optically pure forms of **3** (87%), which are stereospecically converted to the corresponding crotylboranes **10** (94−95%). These reagents undergo the clean addition to even hindered aldehydes in <3 h at −78 °C. Asymmetric crotylboration with **10** may be conducted with or without its isolation, and both oxidative and nonoxidative workups have been developed for the process. The latter method provides the recovered chiral borane moiety in the form of the air-stable and recyclable complex **4** (70−80%). The β-methyl homoallylic alcohols **12**−**15** are obtained in good to excellent yields (69−92%) in high dr (>98:2) and ee (94−99%). Through the appropriate choice of the enantiomeric and geometric form of **10**, any and all of the four possible isomers of the product alcohols can be prepared in a predictable manner. Efficient with respect to both the borane and the "allyl" source, asymmetric allyl- and crotylations with **1** and **10**, respectively, provide attractive alternatives to existing reagents and processes.

Acknowledgment. Dedicated to the memory of Professor Herbert C. Brown. The support of the NSF (CHE0217550), NIH (S06GM8102), and the Department of Education GAANN Program (P200A030197-04) is gratefully acknowledged.

Supporting Information Available: Full experimental procedures, analytical data, and selected spectra for **1**−**15** and derivatives (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA043612I