Notes

Homologation of Boronic Esters with (Dialkoxymethyl)lithiums. Asymmetric Synthesis of α-Alkoxy Boronic Esters†

Laurence Carmès,‡ François Carreaux,* and Bertrand Carboni

Université Rennes-I, Synthèse et Electrosynthèse organiques, UMR 6510 associée au CNRS, campus de Beaulieu, 35042 Rennes Cedex, France

francois.carreaux@univ-rennes1.fr

Received March 27, 2000

Introduction

This past decade has witnessed an increased interest in the chemistry of the α-heterosubstituted boronic acids and esters. Boronic acid analogues of α-amino acids represent an interesting class of enzyme inhibitors. The main results have been hitherto in the field of serine and threonine proteases.[1] We have focused our attention on the α-alkoxy derivatives because of their synthetic interests. This class of compounds is useful for the synthesis of chiral aldehydes[2] and α-amino boronic acids.[3] The addition of α-alkoxy allylboronates to aldehydes leads to homoallyl alcohols with good selectivity[4] and this reaction was used in the total synthesis of the denticulatins.[5] It was also demonstrated that the alkoxy substituents are compatible with chain extension processes.[6] This strategy has been extensively employed in syntheses of biologically important molecules including pheromones[7] and sugars.[8] Moreover, considering the similarity of this class of compounds to α-hydroxy acids, their biological activities are interesting, but has so far received little attention (Figure 1).

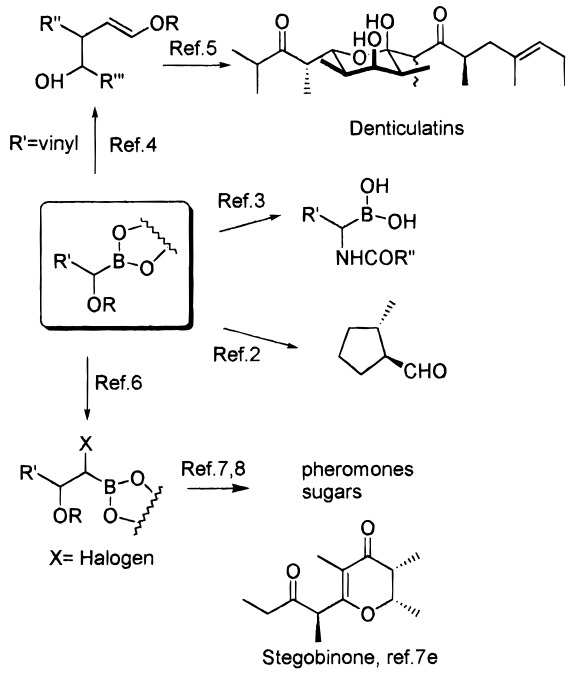


Figure 1. Synthetic interest of α-alkoxy boronic esters as reagents.

Different methods are reported for the synthesis of α-alkoxy boronic esters.[9] The most used strategy is the substitution of α-chloro boronic esters by a lithium alkoxide.[10] Matteson developed an elegant asymmetric synthesis of the α-chloro boronic esters by homologation of boronic esters.[11] When pinanediol is used as the chiral director, the α-chloro derivatives are obtained with high diastereoselectivity for the majority of boronates, except for arylboronates. For example, pinanediol phenylboronate often provides lower de's (88%)[12] than other boronates due to the well-documented epimerization of the resulting benzylic α-chloro boronates in the presence of LiCl.[13] During the substitution of the α-chloro allylboronic esters, a low stereoselectivity can be observed, the result of the epimerization of the α-chloro derivatives by

* To whom correspondence should be addressed. Fax: (33) 2 99 28 69 78.

† A part of this work was presented at the Journées de Chimie Organique, Société Française de Chimie, Palaiseau (France), September 1998, abstract A-169.

‡ Current address: Department of Chemistry, King's Buildings, West Mains Road, Edinburgh EH9 3JJ.

(1) For a review of serine protease inhibitor, see: Hiratake, J.; Oda, J. *Biosci. Biotech. Biochem*. **1997**, *61*, 211−218. Threonine protease inhibitor: Adams, J.; Behnke, M.; Chen, S.; Cruickshank, A. A.; Dick, L. R.; Grenier, L.; Klunder, J. M.; Ma, Y.-T.; Plamondon, L.; Stein, R. L. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 333−338.

(2) Brown, H. C.; Imai, T.; Desai, M. C.; Singaram, B. *J. Am. Chem. Soc.* **1985**, *107*, 4980−4983.

(3) Carmès, L.; Carreaux, F.; Carboni, B.; Mortier, J. *Tetrahedron Lett*. **1998**, *39*, 555−556.

(4) (a) Hoffmann, R. W.; Dresely, S. *Chem. Ber*. **1989**, *122*, 903−909. (b) Hoffmann, R. W.; Wolff, J. J. *Chem. Ber*. **1991**, *124*, 563−569.

(5) Andersen, M. W.; Hildebrandt, B.; Dahmann, G.; Hoffmann, R. W. *Chem. Ber*. **1991**, *124*, 2127−2139.

(6) Matteson, D. S. *J. Organomet. Chem*. **1999**, *581*, 51−65.

(7) (a) Matteson, D. S.; Sadhu, K. *J. Am. Chem. Soc.* **1983**, *105*, 2077−2078. (b) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810−819. (c) Tripathy, P. B.; Matteson, D. S. *Synthesis* **1990**, 200−206. (d) Matteson, D. S.; Man, H.-W. *J. Org. Chem*. **1993**, *58*, 6545−6547. (e) Matteson, D. S.; Man, H.-W.; Ho, O. C. *J. Am. Chem. Soc.* **1996**, *118*, 4560−4566.

(8) (a) Matteson, D. S.; Peterson, M. L. *J. Org. Chem*. **1987**, *52*, 5116−5121. (b) Matteson, D. S.; Kandil, A. A.; Soundararajan, R. *J. Am. Chem. Soc.* **1990**, *112*, 3964−3969.

(9) (a) From α-alkoxyorganostannanes: ref 2. (b) By homologation of boronic esters: Brown, H. C.; Imai, T. *J. Am. Chem. Soc.* **1983**, *105*, 6285−6289. (c) From (1-methoxyvinyl)lithium: Matteson, D. S.; Beedle, E. C. *Heteroatom Chem*. **1990**, *1*, 135−140. (d) From (α-alkoxy allyl)-lithium: Moret, E.; Schlosser, M. *Tetrahedron Lett*. **1984**, *25*, 4491−4494.

(10) (a) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7590−7591. (b) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529−1535. (c) Matteson, D. S.; Kandil, A. A. *J. Org. Chem*. **1987**, *52*, 5121−5124. (d) Matteson, D. S.; Soundararajan, R.; Ho, O. C.; Gatzweiler, W. *Organometallics* **1996**, *15*, 152−163.

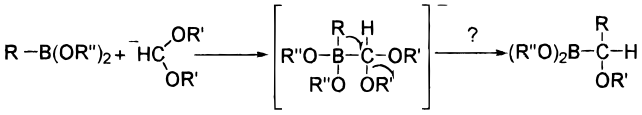
(11) (a) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590−7591. (b) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. *Organometallics* **1983**, *2*, 1536−1543.

(12) Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem*. **1991**, *56*, 3286−3294.

(13) Matteson, D. S.; Erdik, E. *Organometallics* **1983**, *2*, 1083−1088.

10.1021/jo000457r CCC: $19.00
Published on Web 07/11/2000

Scheme 1



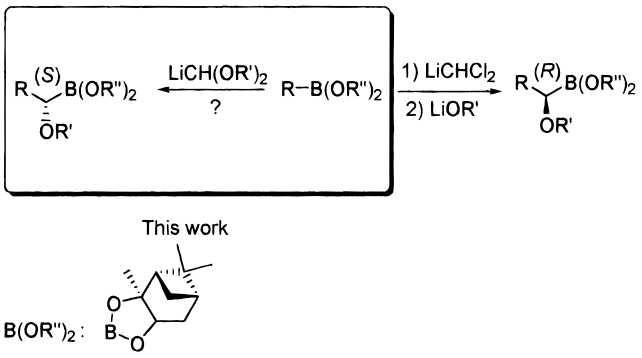
lithium chloride liberated during the slow reaction with alkoxide.[14] In light of these facts and due to the potential of this class of compounds as reagents and as biological tools, we have initiated a program to develop alternative routes to chiral α-alkoxy boronic esters.

Strategy. A widely used process in organoborane chemistry is the construction of C−C bonds via the migration of an organic group from a tetracoordinated boron atom to an adjacent carbon bearing a leaving group.[15] Different carbenoid reagents bearing a potential leaving group(s) (such heteroatom substituents as halogen, sulfur) at the α position were used for the one-carbon homologation of boronic esters.[16] One of the most successful examples of such transfer reactions is the asymmetric construction of carbon−carbon bonds by treatment of a nonracemic boronic esters with (dichloromethyl)lithium.[17] The diastereotopic differentiation of the chloride groups on an sp^3 carbon is governed by the chirality of the diol moiety in the borate complexes. As indicated earlier, homologation of boronic esters of (+)-or (*S*)-pinanediol with (dichloromethyl)lithium yields (α*S*)-α-chloro boronic esters with excellent diastereomeric purity in most of the cases.

Our objective was to find a simple and straightforward access to chiral α-alkoxy boronic esters. We thus chose as our strategy to insert a CHOR group in the carbon−boron bond of boronic esters. The cleavage of these acetals by nucleophiles is a well-known reaction.[18] We envisioned that the borate intermediate as shown in Scheme 1 could lead to the homologated boronic ester by 1,2-migration of an alkyl group from boron to the adjacent atom with displacement of an alkoxy group. This borate complex could be prepared by treatment of an alkylboronic ester with an acyl anion equivalent such as (dialkoxymethyl)-lithium.

Shiner and co-workers reported two procedures for the preparation of (dialkoxymethyl)lithium reagents by reductive lithiation of phenylthio-substituted compounds or by transmetalation of tri-*n*-butylstannyl derivatives.[19] A large variety of α-stannylacetals has been described[20] and the simplicity of their preparation make them attractive reagents. The reaction of (dialkoxymethyl)-lithium reagents with boronic esters should give access to the α-alkoxy boronic esters in only one step. Furthermore, if the (+)-pinanediol boronates provides the (α*R*)-α-alkoxy boronic esters via the α-chloro derivatives (displacement of chloride proceeds with inversion),[21] then with the same chiral director, we should obtain the corresponding epimers. In this paper, we describe the first results of this methodology (Scheme 2).

Scheme 2



Results and Discussion

In our preliminary investigation concerning the synthetic utility of these reagents in organoborane chemistry, we chose diethoxymethyltributyltin as the starting material because of its availability on a large scale.[22] The (diethoxymethyl)lithium, obtained by transmetalation of the corresponding dialkoxymethyltributyltin with *n*-butyllithium in THF at −100 °C,[23] was treated with (+)-pinanediol[24] phenylboronate **1a** in the absence of a Lewis acid. The resulting solution was warmed to room temperature and stirred overnight. After workup of the reaction, the (+)-pinanediol α-(ethoxy)phenylmethylboronate **4a** was isolated by flash chromatography in 58% yield, with 20% diastereomeric purity (Table 1). Determination of diastereomeric excess was based on the ^{1}H NMR, using integration of the different pinanyl methyl protons (δ = 1.34 and 1.37 ppm). To elucidate the mechanism and to identify the intermediates, the reaction was followed by ^{11}B NMR. At −100 °C, the ^{11}B NMR spectrum of the reaction mixture showed that **1a** (δ +30 ppm) was completely converted to an "ate" complex (**2a**, δ −4), which can be attributed to complexation of the reagent on boron. Upon warming, a new peak appeared (δ +7) with gradual disappearance of the precedent. This

(14) Hoffmann, R. W.; Dresely, S. *Tetrahedron Lett.* **1987**, *28*, 5303−5306.

(15) (a) Matteson, D. S. *Stereodirected Synthesis with organoboranes*; Springer: Berlin, 1995. (b) Vaultier, M.; Carboni, B. *In Comprehensive Organometallic Chemistry II*; Stone, F. G. A., Abel, E. V., Eds.; Pergamon: Oxford, 1995; Vol. 11, pp 191−276.

(16) [Chloro(trimethylsilyl)methyl]lithium: (a) Matteson, D. S.; Majumdar, D. *J. Organomet. Chem.* **1980**, *184*, C41−C43. (b) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 230−236. (c) Tsai, D. J. S.; Matteson, D. S. *Organometallics* **1983**, *2*, 236−241. [Methoxy-(phenylthio)methyl]lithium: Reference 9b. (Chloromethyl)lithium: (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687−1689. (b) Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150−3155. (Bromomethyl)lithium: Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631−632. (Iodomethyl)lithium: Wallace, R. H.; Zong, K. K. *Tetrahedron Lett.* **1992**, *33*, 6941−6944. For a comparative study of different (halomethyl)lithiums, see: (a) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8957−8960. (b) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8961−8964. (1,1-Dichloroethyl)lithium: Matteson, D. S.; Hurst, G. D. *Heteroatom Chem.* **1990**, *1*, 65−74. [(Chloroaryl)-methyl]lithium: Kabalka, G. W.; Li, N.-S.; Yu, S. *Tetrahedron: Asymmetry* **1997**, *8*, 3843−3846.

(17) For reviews, see: (a) Matteson. D. S. *Tetrahedron* **1998**, *54*, 10555−10607. (b) Reference 14a, Chapter 5. (c) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201−212. (d) Matteson, D. S. *Pure Appl. Chem.* **1991**, *63*, 339−344. (e) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535−1551.

(18) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043−1054.

(19) Shiner, C. S.; Tsunoda, T.; Goodman, B. A.; Ingham, S.; Lee, S.-H.; Vorndam, P. E. *J. Am. Chem. Soc.* **1989**, *111*, 1381−1392.

(20) Duchêne, A.; Boissière, S.; Parrain, J. L.; Quintard, J.-P. *J. Organomet. Chem.* **1990**, *387*, 153−162.

(21) (a) Midland, M. M.; Zopola, A. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 248−249. (b) Matteson, D. S. *Acc. Chem. Res.* **1970**, *3*, 186−193.

(22) (a) Quintard, J.-P.; Elissondo, B.; Pereyre, M. *J. Organomet. Chem.* **1981**, *212*, C31−C34. (b) Quintard, J.-P.; Elissondo, B.; Mouko-Mpegna, D. *J. Organomet. Chem.* **1983**, *251*, 175−187.

(23) Parrain, J. L.; Beaudet, I.; Cintrat, J. C.; Duchêne, A.; Quintard, J.-P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 304−312.

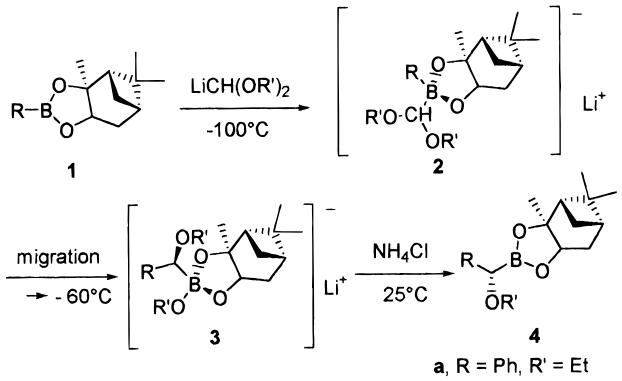
(24) The *Chemical Abstracts* name for (+)- or (*S*)-pinanediol is [1*S*-(1α,2β,3β,5α)]-2,6,6-trimethylbicyclo[3.1.1]heptane-2,3-diol.

Table 1. Homologation of Boronic Esters to α-Alkoxy Boronic Esters

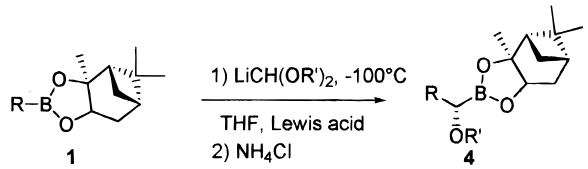
entry	boronic esters	R	R′	Lewis acid (molar ratio)	products (yield,[a] %)	% de[b]
1	**1a**	Ph	Et		**4a** (58)	20
2	**1a**	Ph	Et	$ZnCl_2$ (1)	**4a** (46)	30
3	**1a**	Ph	Et	$ZnCl_2$ (3)	**4a** (65)	≥98
4	**1a**	Ph	Et	$ZnBr_2$ (3)	**4a** (57)	84
5	**1a**	Ph	Et	$BF_3{\cdot}OEt_2$(3)	**4a** (54)	48
6	**1b**	4-BrC_6H_4	Et	$ZnCl_2$ (3)	**4b** (42)	96
7	**1c**	1-naphthyl	Et	$ZnCl_2$ (3)	**4c** (62)	≥98
8	**1d**	1-hexenyl	Et	$ZnCl_2$ (3)	*c*	
9	**1e**	*i*-Pr	Et	$ZnCl_2$ (3)	**4e** (66)	≥98
10	**1f**	*n*-C_6H_{13}	Et	$ZnCl_2$ (3)	**4f** (65)	66
11	**1g**	CH_3	Et	$ZnCl_2$ (3)	**4g** (63)	66
12	**1a**	Ph	Me	$ZnCl_2$ (3)	**4h** (44)	≥98
13	**1g**	CH_3	Me	$ZnCl_2$ (3)	**4i** (40)	64

[a] Isolated yield after flash chromatography. [b] Determined by ^1H NMR and ^{13}C NMR of the crude product. [c] No α-alkoxy boronate was obtained; the major product was hydroxyl pinanediol borate.

Scheme 3



Scheme 4



chemical shift was attributed to an "ate" complex **3a** which results from complexation of the ethoxide, liberated during the 1,2-migration of the phenyl group.[25] This observation is consistent with the rearrangement of **2a** to **3a** taking place between −100 and −60 °C.[26] The product **3a** did not change after standing overnight at room temperature. It is only after addition of a saturated solution of NH_4Cl and extraction with diethyl ether that the α-alkoxy derivative **4a** was obtained. The stability of **3a** is probably due to a strong coordination with boron.[27] The ^{11}B NMR of **4a** showed a peak (δ +31) shifted downfield from the starting material **1a** (Scheme 3).

We then examined the influence of an added Lewis acid (Scheme 4 and Table 1). We were encouraged in this approach by the observation made by Matteson that the yield and the diastereomeric excess of the α-chloro boronic esters improved significantly by addition of Lewis acids, such as zinc chloride.[28] The addition of one equivalent of this Lewis acid did not bring any significant improvement (entry 2). Taking into account that our process takes place with an oxygen-rich reagent, we then decided to add an excess of zinc chloride.[29] The use of 3 equivalents (entry 3) dramatically improved the stereoselectivity of the reaction (de of **4a** ≥98%; ^1H and ^{13}C NMR), but had no effect on the yield. Although the use of an excess of zinc chloride in the homologation with (dichloromethyl)lithium significantly accelerates the epimerization of certain α-chloro boronic esters.[13] This is not a problem with the α-alkoxy analogues.[30] The absolute configuration of the new chiral center of **4**[31] was established unambiguously to be *S* by comparison to the optically pure diastereomer of **4e**[32] using NMR spectroscopy.

To find a better procedure, we tested the effects of several other Lewis acids capable of promoting the rearrangement of **2** to **3**. We then adopted the rule of thumb that one equivalent of Lewis acid would be added for each alkoxy group, plus one equivalent for the rearrangement of **2** to **3**. We initially tested zinc bromide, a more oxophilic Lewis acid than zinc chloride. A diminution of the diastereomeric excess was observed, 84% instead of ≥98% (entry 4). We then tested the effect on the stereoselectivity of a monodentate Lewis acid such as $BF_3.OEt_2$. The preferred stereochemistry is the same as with a bidentate Lewis acid, but a dramatic drop of the diastereomeric excess was observed (entry 5). However, it is interesting to note that the diastereoselectivity was improved compared to the reaction performed without Lewis acid. Although it is a monodentate Lewis acid, the preferential displacement of one of the prochiral alkoxide groups is again favored.

After identifying the best Lewis acid, we then extended this process catalyzed by zinc chloride to other boronic esters. We initially examined arylboronic esters. We have been agreeably surprised to observe that in all the cases examined, high diastereoselectivities were obtained (entries 6 and 7). It is important to note that the presence

(25) The same chemical shift was observed when **4a** was treated with lithium ethoxide in THF.

(26) The same NMR study was realized with the (+)-pinanediol methylboronate **1g**. The migration of the methyl group was observed at an upper temperature to −60 °C.

(27) B−O; $\Delta H_{f25}° = 188$ kcal mol^{-1}. Dean, J. A. Ed. *Lange's Handbook of Chemistry, Thirteenth Edition*; MacGraw-Hill: New York, 1985; pp 3−128.

(28) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077−2078.

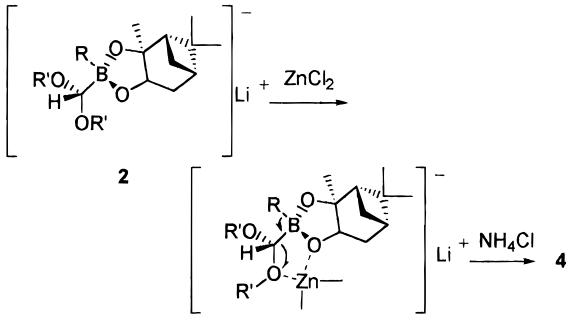
(29) An excess of zinc chloride is also required during the Matteson homologation with compounds containing oxygen functionality. Reference 8a.

(30) A mixture of **4a**, lithium ethoxide and zinc chloride in THF was stirred overnight at room temperature. No detectable epimerization is observed only a small degradation of the product (∼2%).

(31) Systematic names of **4**: **4a**, {3a*S*-[2(*R**),3aα,4*β*,6*β*,7aα]}-2-[1-(ethoxy)phenylmethyl]hexahydro-3a,5,5-trimethyl-4−6-methano-1,3,2-benzodioxaborole; **4b**, {3a*S*-[2(*R**),3aα,4*β*,6*β*,7aα]}-2-[1-(ethoxy)(4-bromophenyl)methyl]hexahydro-3a,5,5-trimethyl-4−6-methano-1,3,2-benzodioxaborole; **4c**, {3a*S*-[2(*R**),3aα,4*β*,6*β*,7aα]}-2-[1-(ethoxy)(1-naphthyl)methyl]hexahydro-3a,5,5-trimethyl-4−6-methano-1,3,2-benzodioxaborole; **4e**, {3a*S*-[2(*R**),3aα,4*β*,6*β*,7aα]}-2-[1-(ethoxy)-2-methylethyl]hexahydro-3a,5,5-trimethyl-4−6-methano-1,3,2-benzodioxaborole; **4f**, {3a*S*-[2(*R**),3aα,4*β*,6*β*, 7aα]}-2-[1-(ethoxy)-heptyl]hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole; **4g**, {3a*S*-[2(*R**),3aα,4*β*,6*β*,7aα]}-2-[1-(ethoxy)ethyl]hexahydro-3a,5,5-trimethyl-4−6-methano-1,3,2-benzodioxaborole; **4h**, {3a*S*-[2(*R**),-3aα,4*β*,6*β*,7aα]}-2-[1-(methoxy)phenylmethyl]hexahydro-3a,5,5-trimethyl-4−6-methano-1,3,2-benzodioxaborole; **4i**, {3a*S*-[2(*R**),3aα,4*β*,6*β*,7aα]}-2-[1-(methoxy)ethyl]hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole. The 3a*S* designates the absolute configuration of the entire molecule by reference to carbon 3a. The 2(*R**) indicates that this is the enantiomer in which the side chain at position 2 would have the *R* configuration if position 3a were *R*, but since position 3a is *S*, the side chain is *S*.

(32) The diastereoisomer of **4e** was obtained by substitution of (+)-pinanediol-(1*S*)-1-chloro-2-methylpropylboronate[7a] with lithium ethoxide.

Scheme 5



of a bromine atom on the aryl ring was tolerated under these conditions. We have not observed byproducts resulting from lithium−halogen exchange. A disappointing result was obtained with the vinylboronate **1d** given that the expected product was not isolated (entry 8). The major product was hydroxyl pinanediol borate which may be the result of decomposition catalyzed by $ZnCl_2$.[33] Isopropylboronate gave the α-alkoxy derivative **4e** in ≥98% de (entry 9) while the *n*-alkylboronates produced the corresponding product in 66% de (entries 10, 11). Clearly, our results indicates that the de of the final product **4** is dependent upon R. In addition to steric effects, the high diastereoselectivity obtained with arylboronates may be explained partially by the high migratory aptitude of the aryl groups compared to the *n*-alkyl groups.[34]

We have also experimented (dimethoxymethyl)lithium in our homologation reaction. The results are similar with those obtained with (diethoxymethyl)lithium except the yields are lower (entries 12, 13). It should be noted that even at −100 °C, the reaction does not take place using the dibenzyloxymethyltributyltin, presumably due to the higher acidity of the benzylic proton which preclude the formation of the prerequisite (dibenzyloxymethyl)lithium.[35]

From a mechanistic point of view, taking into account the absolute configuration of the final product, it can be proposed that the reaction proceeds as depicted in Scheme 5. According to the litterature,[36] we believe that the dialkoxymethyllithium reagent adds to the (+)-pinanediol boronate exclusively on the less sterically hindered side of the boron atom. We can deduce that the reaction involves complexation of a Lewis acid with one of the two oxygens of the boronic ester and that the Lewis acid then assists one of the two prochiral alkoxide groups in leaving. The migration is then carried out in an S_N2 manner, anti to the departing oxygen. Although the reactions are different, we were consolidated on this interpretation by the fact that we obtained the same configuration as during the homologation with $LiCHCl_2$.[37]

Conclusions

In this paper, we have developed a new homologation reaction of boronic esters with (dialkoxymethyl)lithium reagents. This new process provides a convenient and one-step method to obtain the α-alkoxy boronic esters. When the reaction is catalyzed by zinc chloride, a high diastereoselection has been obtained from aryl and *sec*-alkylboronates (≥98%).

This new procedure complements the existing methodology described by Matteson, making it possible to synthesize both (1*R*)- and (1*S*)-alkoxy boronic esters with the same chiral director. With the ready availability of (dialkoxymethyl)lithium reagents, this method should be adaptable to the synthesis of a wide variety of α-alkoxy boronic esters. Studies to further examine the origin of the stereoselectivity, scope and limitations of the methodology are currently under investigation.

Experimental Section

General Procedures. Reactions were performed in oven-dried glassware under an argon atmosphere. Tetrahydrofuran (THF) was distilled from deep blue solutions of sodium/benzophenone ketyl prior to use. *n*-BuLi, 1.6 M in hexane, purchased from Aldrich Chemical Co., Inc., was titrated as indicated by Watson and Eastham.[38] $ZnCl_2$ was vacuum-dried at 100 °C/0.1 Torr. All boronic acids were purchased (Lancaster Synthesis Ltd) except 1-(methyl)ethylboronic acid,[39] hexylboronic acid[40] and 1-hexenylboronic acid.[41] The (+)-pinanediol (used as purchased from Aldrich Company) was 98% ee. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ on a 200- or 300-MHz spectrometer operating in the Fourier transform mode. ^{13}C NMR spectra were obtained with broadband proton decoupling. Chemical shifts were recorded relative to the internal TMS (tetramethylsilane) reference signal. For ^{11}B NMR, the chemical shifts are in ppm relative to $BF_3{\cdot}OEt_2$. Optical rotations were measured using 10-cm cell at 20 °C, and the concentration is expressed in g/dL. HRMS were performed by Centre Régional de Mesures Physiques de l'Ouest. Microanalysis were done at the Central Laboratory for Analysis, CNRS, Lyon, (France). Silica gel 60F254 was used for column chromatography.

(+)-Pinanediol Boronic Esters. A solution of (+)-pinanediol and 1.1 equivalent of the boronic acid in ether was stirred overnight at room temperature. The organic phase was washed with water, dried over magnesium sulfate, concentrated, and the boronic ester was chromatographied or recrystallized. The NMR and analytical data of **1a**, **1g**,[11b] and **1e**[42] have been reported.

(+)-Pinanediol (4-bromophenyl)boronate (1b): mp 83−85 °C; 95% (R_f = 0.4, heptane: ethyl acetate 95:5); $[\alpha]^{20}_D$ +7.6 (*c* 1.0 in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.44 (dd, *J* = 1.8, 8.7 Hz, 1H), 2.41−1.92 (m, 5H), 1.47 (s, 3H), 1.31 (s, 3H), 1.17 (d, *J* = 10.6 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.3, 131.0, 126.2, 86.5, 78.4, 51.4, 39.5, 38.2, 35.5, 28.7, 27.1, 26.5, 24.0; HRMS (EI) calcd for $C_{16}H_{20}BBrO_2$ (M^+) 334.0739, found 334.0739. Anal. Calcd for $C_{16}H_{20}BBrO_2$: C, 57.36; H, 6.02. Found: C, 57.32; H, 6.07.

(+)-Pinanediol (1-naphthyl)boronate (1c): mp 73−75 °C; 98% (R_f = 0.28, heptane: ethyl acetate 95:5); $[\alpha]^{20}_D$ +5.1 (*c* 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (m, 1H), 8.08 (dd, *J* = 1.4, 6.8 Hz, 1H), 7.93 (dd, *J* = 1.4, 8.2 Hz, 1H), 7.83 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.54−7.44 (m, 3H), 4.55 (dd, *J* = 1.9, 8.7 Hz, 1H), 2.47−1.97 (m, 5H), 1.56 (s, 3H), 1.34 (m, 3H), 1.29 (s, 1H), 0.93 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.9, 135.7, 133.2,

(33) The α-ethoxy derivative **4d** was obtained from the (+)-pinanediol 1-hexenylboronate without Lewis acid in 14% de, yield 50%.

(34) No quantitative study of migratory aptitudes was carried out in homologation reaction, contrary to the oxidative deboronation. However, certain brief replies are given in the ref 15a.

(35) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763−773.

(36) Tsai, D. J. S.; Jesthi, P. K.; Matteson, D. S. *Organometallics* **1983**, *2*, 1543−1545.

(37) (a) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3711−3713. (b) Midland, M. *J. Org. Chem.* **1998**, *63*, 914−915.

(38) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165−168.

(39) Brown, H. C.; Srebnik, M.; Cole, T. E. *Organometallics* **1986**, *5*, 2300−2303.

(40) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1980**, *45*, 384−389.

(41) Brown, H. C.; Campbell, J. B. *J. Org. Chem.* **1980**, *45*, 389−395.

(42) Matteson, D. S.; Jesthi, P. K.; Sadhu, K. M. *Organometallics* **1984**, *3*, 1284−1288.

131.5, 128.4, 128.3, 126.3, 125.5, 125.0, 86.1, 78.1, 51.5, 39.6, 35.7, 28.8, 28.2, 27.1, 26.6, 24.0; ^{11}B NMR (96 MHz, $CDCl_3$) δ 30.7; HRMS (EI) calcd for $C_{20}H_{23}BO_2$ (M^+) 306.1791, found 306.1784. Anal. Calcd for $C_{20}H_{23}BO_2$: C, 78.45; H, 7.57. Found: C, 78.54; H, 7.49.

(+)-Pinanediol 1-hexenylboronate (1d): oil; 95% (R_f = 0.21, heptane: ethyl acetate 99:1); $[\alpha]^{20}_D$ +17.1 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.64 (dt, *J* = 18.0, 6.4 Hz, 1H), 5.45 (dt, *J* = 18.0, 1.4 Hz, 1H), 4.29 (dd, *J* = 8.7, 1.6 Hz, 1H), 2.25−1.84 (m, 7H), 1.44−1.34 (m, 4H), 1.40 (s, 3H), 1.29 (s, 3H), 1.15 (d, *J* = 10.8 Hz, 1H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.0, 85.1, 78.0, 51.8, 39.9, 38.5, 35.9, 30.8, 29.0, 27.5, 26.8, 26.7, 24.4, 22.6, 14.3; HRMS (EI) calcd for $C_{16}H_{27}BO_2$ (M^+) 262.2104, found 262.2108. Anal. Calcd for $C_{16}H_{27}BO_2$: C, 73.29; H, 10.38. Found: C, 73.18; H, 10.31.

(+)-Pinanediol hexylboronate (1e): oil; 94% (R_f = 0.26, heptane); $[\alpha]^{20}_D$ +5.1 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.25 (dd, *J* = 1.8, 8.6 Hz, 1H), 2.32−1.80 (m, 5H), 1.38 (s, 3H), 1.35 (m, 8H), 1.29 (s, 3H), 1.12 (d, *J* = 10.7 Hz, 1H), 0.90−0.77 (m, 5H), 0.84 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 85.2, 77.7, 51.3, 39.6, 38.1, 35.6, 32.2, 31.7, 28.7, 27.1, 26.5, 24.1, 24.0, 22.6, 14.1. Anal. Calcd for $C_{16}H_{29}BO_2$: C, 72.73; H, 11.06. Found: C, 72.80; H, 11.15.

General Procedure for Reaction of (Dialkoxymethyl)-lithiums with Boronic Esters in the Presence of Zinc Chloride. A solution of dialkoxymethyltributyltin (0.89 mmol) in 2 mL of THF was cooled to −100 °C in a 95% ethanol/liquid nitrogen bath and stirred magnetically during the dropwise addition of 1.07 mmol of *n*-butyllithium (1.6 M in hexane). After 15−20 min at −100 °C, a solution of 0.89 mmol of the boronic esters **1** in 1 mL of THF was added slowly, and then the solution of anhydrous zinc chloride (0.27 mmol) in 2−3 mL of THF was added. The mixture was allowed to warm to room temperature slowly and stirred overnight. The reaction mixture was quenched with 5 mL of saturated aqueous NH_4Cl and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with brine, dried over magnesium sulfate, filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (210−400 mesh), initially with 100% heptane to remove tin byproducts, followed by 1−5% ethyl acetate/heptane gradient elution.

(*S*)-Pinanediol (1*S*)-[1-(ethoxy)phenylmethyl]boronate (4a): oil; 65% (R_f = 0.25, heptane/ethyl acetate 95:5); $[\alpha]^{20}_D$ −53.6 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.18 (m, 5H), 4.33 (s, 1H), 4.29 (dd, *J* = 2.0, 8.8 Hz, 1H), 3.59−3.30 (m, 2H), 2.33−1.66 (m, 5H), 1.34 (s, 3H), 1.24 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.90 (m, 1H), 0.80 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.3, 127.3, 126.0, 125.7, 85.4, 77.3, 64.4, 50.1, 38.2, 37.1, 34.2, 27.3, 26.0, 25.1, 22.9, 14.3; ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.0; HRMS (EI) calcd for $C_{19}H_{27}BO_3$ (M^+) 314.2053, found 314.2067. Anal. Calcd for $C_{19}H_{27}BO_3$: C, 72.62; H, 8.66. Found: C, 72.70; H, 8.80. An epimeric mixture, prepared without a Lewis acid, showed the presence of additional peaks in the ^{1}H NMR ((1*R*) δ 1.37) and ^{13}C NMR ((1*R*) δ 64.2 and 24.9). No evidence of the epimer was seen in the sample of **4a**.

(*S*)-Pinanediol (1*S*)-[1-(ethoxy)(4-bromophenyl)methyl]-boronate (4b): oil; 42% (R_f = 0.18, heptane/ethyl acetate 95:5); $[\alpha]^{20}_D$ −6.0 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47−7.19 (m, 4H), 4.29 (dd, *J* = 2.0, 8.6 Hz, 1H), 4.28 (s, 1H), 3.49 (qd, *J* = 7.0, 9.5 Hz, 1H), 3.38 (qd, *J* = 7.0, 9.5 Hz, 1H), 2.35−1.39 (m, 5H), 1.37 (epimer 2%), 1.34 (s, 3H), 1.25 (s, 3H), 1.20 (t, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 10.1 Hz, 1H), 0.80 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6, 131.4, 128.5, 120.4, 86.6, 78.4, 65.6, 51.2, 39.3, 38.1, 35.2, 28.4, 27.0, 26.2, 24.0, 15.3; ^{11}B NMR (96 MHz, $CDCl_3$) δ 30.9. Anal. Calcd for $C_{19}H_{26}BO_3Br\cdot 0.7H_2O$: C, 56.24; H, 6.81. Found: C, 56.21; H, 6.57. The position of the epimer peak was verified by the synthesis of **4b** without a Lewis acid.

(*S*)-Pinanediol (1*S*)-[1-ethoxy(1-naphthyl)methyl]boronate (4c): oil; 62% (R_f = 0.16, heptane/ethyl acetate 95:5); $[\alpha]^{20}_D$ −22.1 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37−8.32 (m, 1H), 7.88−7.75 (m, 2H), 7.56−7.40 (m, 4H), 4.88 (s, 1H), 4.32 (dd, *J* = 2.0, 8.8 Hz, 1H), 3.53−3.32 (m, 2H), 2.18−1.61 (m, 5H), 1.29 (s, 3H), 1.22 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.98 (m, 1H), 0.78 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.3, 133.9, 131.6, 128.4, 127.7, 125.9, 125.6, 125.5, 125.4, 124.9, 86.7, 78.4, 65.3, 51.0, 39.2, 38.1, 35.2, 28.4, 27.0, 26.3, 23.9, 15.4; ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.5; HRMS (EI) calcd for $C_{21}H_{24}BO_3$ (M^+ − C_2H_5) 335.1818, found 335.1827. Anal. Calcd for $C_{23}H_{29}BO_3$: C, 75.83; H, 8.02. Found: C, 75.77; H, 8.13. An epimeric mixture, prepared without a Lewis acid, showed the presence of additional peaks in the ^{1}H NMR ((1*R*) δ 4.87, 4.30, 1.38, 0.72). No evidence of the epimer was seen in the sample of **4c**.

(*S*)-Pinanediol (1*S*)-[1-(ethoxy)-2-methylpropyl]boronate (4e): oil; 66% (R_f = 0.19, heptane/ethyl acetate 97:3); $[\alpha]^{20}_D$ +32.8 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (dd, *J* = 2.2, 8.8 Hz, 1H), 3.53 (qd, *J* = 6.9, 9.1 Hz, 1H), 3.43 (qd, *J* = 6.9, 9.1 Hz, 1H), 2.97 (d, *J* = 6.4 Hz, 1H), 2.42−1.83 (m, 6H), 1.40 (s, 3H), 1.29 (s, 3H), 1.20 (t, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 10.3 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 86.1, 77.9, 66.3, 51.1, 39.5, 38.1, 35.5, 30.5, 28.8, 27.1, 26.7, 24.1, 19.6, 19.5, 15.6; ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.85; HRMS (EI) calcd for $C_{14}H_{24}BO_3$ (M^+ − C_2H_5) 251.1818, found 251.1818. Anal. Calcd for $C_{16}H_{29}BO_3$: C, 68.58; H, 10.43. Found: C, 68.31; H, 10.46. The position of the epimer peaks was verified by the synthesis of the diastereomer of **4e**:[32] ^{1}H NMR ((1*R*) δ 3.51, 3.46, 1.41, 0.97 instead of 3.53, 3.43, 1.40, 0.98 for (1*S*)); ^{13}C NMR ((1*R*) δ 30.2 and 26.6 instead of 30.5 and 26.7 for (1*S*)). No evidence of the epimer was seen in the sample of **4e**.

(*S*)-Pinanediol (1*S*)-[1-(ethoxy)heptyl]boronate (4f): oil; 65% (R_f = 0.20, heptane: ethyl acetate 95:5); $[\alpha]^{20}_D$ −6.0 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.32 (dd, *J* = 2.0, 8.8 Hz, 1H), 3.53−3.44 (m, 2H), 3.27 (t, *J* = 6.4 Hz, 1H), 2.37−1.86 (m, 5H), 1.71−1.59 (m, 2H), 1.40 (s, 3H), 1.38−1.27 (m, 8H), 1.29 (s, 3H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 10.8 Hz, 1H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.1, 78.0, 65.5, 51.2, 51.1 (epimer 17%), 39.5, 38.1, 35.5, 35.4 (epimer 17%), 31.8, 31.5, 31.3 (epimer 17%), 29.5, 28.7, 27.1, 26.6, 26.5 (epimer 17%), 26.4, 24.0, 22.6, 15.6, 14.1; ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.8. HRMS (EI) calcd for $C_{17}H_{30}BO_3$ (M^+ − C_2H_5) 293.2288, found 293.2276. Anal. Calcd for $C_{19}H_{35}BO_3$: C, 70.81; H, 10.95. Found: C, 71.08; H, 11.01. The position of the epimer peaks was verified by the synthesis of the diastereomer of **4f** via the α-chloro derivative.

(*S*)-Pinanediol (1*S*)-[1-(ethoxy)ethyl]boronate (4 g): oil; 63% (R_f = 0.17, heptane/ethyl acetate 95:5); $[\alpha]^{20}_D$ +30.0 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.32 (dd, *J* = 1.9, 8.9 Hz, 1H), 3.61−3.43 (m, 2H), 3.38 (q, *J* = 7.6 Hz, 1H), 2.37−1.87 (m, 5H), 1.41 (s, 3H), 1.30 (d, *J* = 7.6 Hz, 3H), 1.29 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 10.8 Hz, 1H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.2, 78.1, 65.1, 65.0 (epimer 17%), 51.1, 39.4, 38.1, 35.4, 35.3 (epimer 17%), 28.6, 27.1, 26.5, 26.4 (epimer 17%), 24.0, 16.7, 16.5 (epimer 17%), 15.6; ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.9; HRMS (EI) calcd for $C_{12}H_{20}BO_3$ (M^+ − C_2H_5) 223.1505, found 223.1510. Anal. Calcd for $C_{14}H_{25}BO_3$: C, 66.68; H, 9.99. Found: C, 66.41; H, 10.15. The position of the epimer peaks was verified by the synthesis of the diastereomer of **4g** via the α-chloro derivative.

(*S*)-Pinanediol (1*S*)-[1-(methoxy)phenylmethyl]boronate (4h): oil; 44% (R_f = 0.23, heptane/ethyl acetate 90:10); $[\alpha]^{20}_D$ −69.8 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27−7.15 (m, 5H), 4.22 (dd, *J* = 2.0, 8.7 Hz, 1H), 4.12 (s, 1H), 3.21 (s, 3H), 2.17−1.60 (m, 5H), 1.29 (s, 3H), 1.17 (s, 3H), 0.84 (d, *J* = 10.2 Hz, 1H), 0.73 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.6, 127.4, 126.1, 125.9, 85.5, 77.3, 57.0, 50.1, 38.3, 37.1, 34.1, 27.4, 26.0, 25.1, 22.9; ^{11}B NMR (96 MHz, $CDCl_3$) δ 30.6; HRMS (EI) calcd for $C_{18}H_{25}BO_3$ 300.1897, found 300.1914. Anal. Calcd for $C_{18}H_{25}BO_3$: C, 72.02; H, 8.39. Found: C, 72.06; H, 8.41. An epimeric mixture, prepared without a Lewis acid showed the presence of additional peaks in the ^{1}H NMR ((1*R*) δ 3.20 and 1.30). No evidence of the epimer was seen in the sample of **4h**.

(*S*)-Pinanediol (1*S*)-[1-(methoxy)ethyl]boronate (4i): oil; 40% (R_f = 0.18, heptane/ethyl acetate 90:10); $[\alpha]^{20}_D$ +28.0 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.25 (dd, *J* = 1.8, 8.7 Hz, 1H), 3.30 (s, 3H), 3.21 (q, *J* = 7.5 Hz, 1H), 2.29−1.79 (m, 5H), 1.35 (s, 3H), 1.24 (d, *J* = 7.5 Hz, 3H), 1.22 (s, 3H), 1.06 (d, *J* = 10.8 Hz, 1H), 0.77 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 86.4, 86.3 (epimer 18%), 78.2, 57.6, 51.1, 39.4, 38.1, 35.4, 35.3 (epimer 18%), 28.6, 27.1, 26.5, 24.0, 15.9, 15.7 (epimer 18%); ^{11}B NMR (96 MHz, $CDCl_3$) δ 31.8; HRMS (EI) calcd for $C_{12}H_{20}BO_3$ (M^+ − CH_3) 223.1505, found 223.1465. Anal. Calcd for $C_{13}H_{23}BO_3$: C, 65.57; H, 9.74. Found: C, 65.73; H, 9.99. The position of the

epimer peaks was verified by the synthesis of the diastereomer of **4i** via the α-chloro derivative.

Acknowledgment. Financial support from the CNRS and a doctoral fellowship from "Conseil Régional de Bretagne" to L.C. are gratefully acknowledged. Wethank Prof. D. S. Matteson for fruitful discussions at the time of his stay in Rennes as invited Professor, and, too, Prof. J. P. Quintard. In addition, we thank S. Sinbandhit for running the NMR spectra.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **4a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000457R