Novel Functionalized Trisubstituted Allylboronates via Hosomi−Miyaura Borylation of Functionalized Allyl Acetates
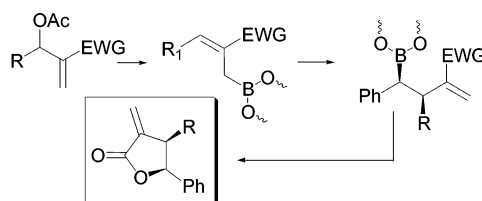
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ABSTRACT

A series of novel functionalized achiral and chiral allylboronates have been synthesized via the nucleophilic addition of boronates on allyl acetates derived via vinylalumination or Baylis−Hillman reaction of aldehydes. These reagents, upon allylboration with aldehydes, furnish β-substituted-α-methylene-γ-butyrolactones stereoselectively.

Since the initial discovery by Mikhailov and Bubnov,[1] allylboration has become one of the extremely important C−C bond-forming reactions for the stereoselective synthesis of homoallylic alcohols.[2] Extensive work by Hoffmann[3] and Roush[4] on allylboronates and by Brown[5] on allylboranes has led to the development of various organoborane reagents. Many of these reagents have become invaluable tools in the arsenal of organic chemists for the total synthesis of complex natural products.[6]

For the past few years we have been developing the vinylalumination (VA) reaction for the synthesis of functionalized allyl alcohols.[7] Similar types of products can also be obtained via Baylis−Hillman (BH) reaction.[8]

Hosomi[9] and Miyaura[10] have independently reported the 1,4-addition of nucleophilic boryl copper species generated in situ from diboronates to simple α,β-unsaturated carbonyl compounds. Our longstanding tradition in the area of

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organoborane chemistry[11] and current projects involving vinylalumination[7] of carbonyl compounds prompted us to investigate the SN2′-type addition of boronates on the acetates derived from VA or BH product alcohols. We envisaged a novel class of functionalized allylboronates by the nucleophilic addition of boryl copper species to the allylic acetates with a concomitant elimination of the acetates. The successful synthesis of such allylboronates and the subsequent allylboration study are reported herein.

For the present study, several representative allyl acetates **3−4** were prepared via the vinylalumination of aldehydes, followed by the esterification of the resulting alcohols with Ac_2O and pyridine (Scheme 1). We chose three commercially

Scheme 1
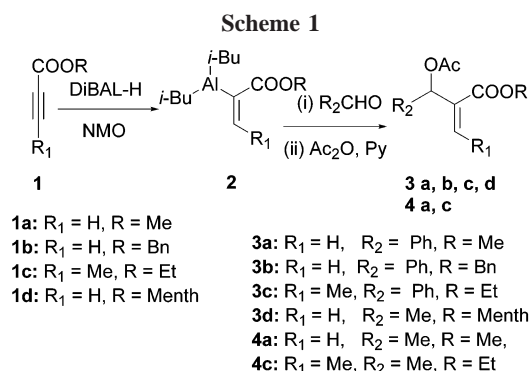
available diboron compounds, viz., bispinacolatodiboron **5**, bis(pinanediolato)diboron **6**, bis(diethyl-L-tartarate glycollato)diboron **7**, for the generation of nucleophilic boronates (Figure 1).
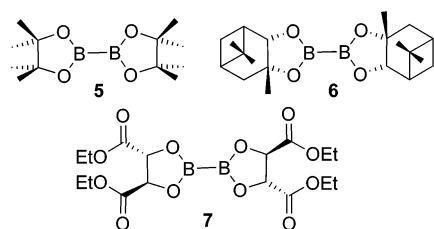

Figure 1.

The reaction of **3a** with **5** under Miyaura conditions[10] took place smoothly in SN2′ fashion with allylic rearrangement and the elimination of the acetate to provide **8a** in 88% yield. The same reaction under Hosomi conditions[9] employing CuOTf and PBu$_3$ was also very facile and **8a** was obtained in 86% yield (Table 1). We opted for Miyaura conditions

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(11) (a) Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23. (b) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16. (c) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1991**, *62*, 307.

Table 1. Asymmetric Allylboration of Benzaldehyde with Allylboronates Derived via SN2′-Borylation
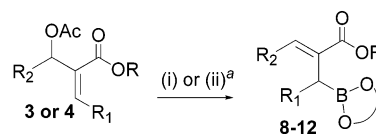
acetate no.	(B(OR)$_2$)$_2$ no.	rxn cond[a]	allylboronate		
			no.	yield, %	E/Z
3a	**5**	M	**8a**	88	>95/<5
3a	**5**	H	**8a**	86	>95/<5
3b	**5**	M	**8b**	97	>95/<5
3c	**5**	M	**8c**	84	>95/<5
4a	**5**	M	**9a**	85	90/10
4c	**5**	M	**9c**	96	88/12
3d	**5**	M	**9d**	76	94/6
3a	**6**	M	**10a**	99	>95/<5
3c	**6**	M	**10c**	70	>95/<5
4a	**6**	M	**11a**	98	>95/<5
4a	**7**	H	**12a**	b	

[a] M = Miyaura conditions: CuCl, LiCl, KOAc, DMF. H = Hosomi conditions: CuCl or (CuOTf)$_2$·C$_6$H$_6$, Bu$_3$P, DMF. [b] The reagent was generated in situ and used without further purification in the next step.

since it employs simpler reagents, such as LiCl and KOAc. The reaction of acetate **4a** with **5** provided the allylboronate **9a** in 85% yield. The crude NMR analysis of the boronates **8a** and **9a** revealed the isomeric purity of the double bond to be >90% (*E*). These boronates are quite stable and could be readily purified by silica gel chromatography.[12] The acetates **3c** and **4c** contain a methyl group β to the ester group and the reactions were slow. However, the yield of the allylboronates **8c** and **9c** were high. The acetate **3d** containing menthol as a chiral auxiliary also reacted in a facile manner and the chiral allylboronate **9d** was isolated in 76% yield. The preparation of various allylboronates is summarized in Table 1.

We decided to incorporate tartarate-based boronates **12a** since the presence of two ester groups should make boron more electrophilic and, consequently, more reactive. Moreover, tartarate is C_2-symmetric and hence will reduce the number of competitive diastereomeric transition states in the allylboration reaction. However, the reaction of **7** with **4a** under Miyaura conditions did not proceed smoothly and the

(12) **General procedure for the preparation of allylboronates under Miyaura conditions:** A mixture of CuCl (1.4 mmol) and LiCl (1.4 mmol) in DMF (2 mL) was stirred under N$_2$ for 1 h at 25 °C and diboron species **5** or **6** (1.4 mmol) dissolved in DMF (2 mL) was added to it. KOAc (1.4 mmol) was added to the reaction mixture followed by the addition of allyl acetates **3−4** (1.0 mmol) dissolved in DMF (1 mL). The reaction mixture was further stirred for 3−5 h. (In the case of β-substituted acetates, the reaction mixture was stirred for 3 d and all the reagents were taken in 3.5 equiv.) The reaction mixture was then quenched with water and extracted with ether (3 × 20 mL). The combined organic layers were dried (MgSO$_4$), concentrated under vacuum, and purified by column chromatography (silica gel, hexanes:ethyl acetate) to obtain 50−99% yields of **8−11**. ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 6.82 (q, *J* = 7.02 Hz, 1H), 3.70 (s, 3H), 1.85 (s, 2H), 1.77 (d, *J* = 7.05 Hz, 3H), 1.23 (s, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 168.5, 137.8, 135.7, 130.0, 83.3, 51.6, 24.6, 14.5; ^{11}B NMR δ (ppm) 32; EI-MS *m/z* 240 (M)$^+$, 54; CI-MS *m/z* 241 (M + H)$^+$; HRMS-CI 240.1541 (actual), 240.1533 (calcd).

reagent **12a** invariably decomposed under the reaction conditions. Hence we resorted to Hosomi's conditions and allylboronate **12a** could be readily obtained with **7** and PBu₃/CuCl. However, attempts to isolate the allylboronate by aqueous workup led to the quenching of the reagent and hence this reagent was generated and utilized in situ for the next step.

To demonstrate the generality of the preparation of functionalized allylboronates, the reagent bearing a ketone moiety (**14**) was similarly prepared in high yield and selectivity from the corresponding allyl acetate (**13**) (Scheme 2).

Scheme 2 [a]
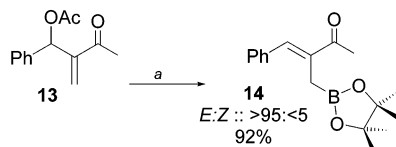
[a] Reagents and conditions: **5**, CuCl, LiCl, KOAc, DMF, 92%.

The allylboronate (**16**) incorporating a nitrile group was prepared from the corresponding allyl acetate **15** derived from the BH reaction of acrylonitrile with acetaldehyde, followed by esterification with acetic anhydride. Reaction of **15** and **5** under Miyaura conditions provided the allylboronate **16**. However, the stereochemistry of the double bond was found to be in the ratio 37:63 (*E:Z*) (Scheme 3).

Scheme 3 [a]
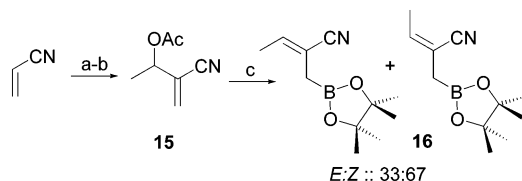
[a] Reagents and conditions: (a) CH₃CHO, DABCO, 78%; (b) Ac₂O, Py, 70%; (c) **5**, CuCl, LiCl, KOAc, DMF, 50%.

The *Z* preference is similar to those reported by Hoffmann and also by Basavaiah[13] with other nucleophiles.

After successfully synthesizing various chiral and achiral allylboronate reagents,[14] we applied them for the allylboration of aldehydes in the synthesis of α-alkylidene-β-substituted-

(13) (a) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213. (b) Basavaiah, D.; Sarma, P. K. S. *J. Chem. Soc., Chem. Commun.* **1992**, 955. (c) Basavaiah, D.; Sarma, P. K. S.; Bhavani, A. K. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1091.

(14) A similar type of boronates have been prepared recently via the reaction of vinyl copper or vinyl aluminium on iodomethylboronate. (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *125*, 898. (b) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *125*, 11586. (c) Chataigner, I.; Lebreton, J.; Zammatio, F.; Villiéras, J. *Tetrahedron Lett.* **1997**, *38*, 3719. (d) For the preparation of allylboronates via cross-metathesis reaction, see: Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807.

γ-butyrolactones.[15] The reaction of **9a** with benzaldehyde in THF was very slow at room temperature and was complete in 7 d. Removal of the solvent, followed by the addition of a catalytic amount of pTSA and refluxing in CH₂Cl₂, converted the intermediate homoallylic alcohol to α-methylene-β-methyl-γ-butyrolactone **17** in 64% yield. Analysis of the crude reaction mixture indicated the diastereomeric mixture to be 84:16 (cis:trans). Refluxing the reaction mixture in THF or heating to 100 °C in toluene shortened the reaction time to 4 d and 1 d, respectively. However, the diastereomeric ratio was found to be essentially similar (Table 2). Allylboration with chiral reagent **9d** also proceeded

Table 2. Asymmetric Allylboration of Benzaldehyde with Allylboronates Derived via SN₂′-Borylation
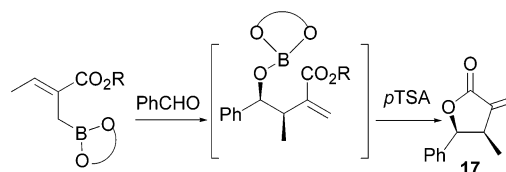
| rgnt no. | rxn condns | | | lactone 17 | | |
	solv	temp, °C	time, d	yield, %	cis:trans	ee,[a] %
9a	THF	25	7	64	84:16	
9a	THF,	70	4	83	85:15	
9a	Tol	100	1	87	87:13	
9d	THF	25	5	50	87:13	25
11a	THF	25	7	75	79:21	10
11a	Tol	100	3	80	83:17	8
12a	DMF	25	2	80	94:6	26
12a	DMF	0	3	52	95:5	27
12a	DMF/THF	−25	6	76	96:4	25
12a	DMF/THF	−78	6	40[b]	94:6	20
12a	DMF/THF[c]	−25	7	56	98:2	21
12a[d]	THF	0	2	75	98:2	22
12a[e]	THF	0	2	69	98:2	19
12a[d]	CH₂Cl₂	0	2	64	98:2	16
12a[e]	CH₂Cl₂[f]	0	2	67	98:2	22
12a[d]	Tol	0	2	74	98:2	25
12a[e]	Tol[f]	0	2	76	98:2	12

[a] % ee was determined on a HPLC, using a Chiralcel-ODH column. Absolute configuration was not determined. [b] 40% of benzaldehyde remained unreacted. [c] In the presence of 30% BF₃−Et₂O. [d] Reagent generated with CuCl and PBu₃. [e] Reagent generated with (CuOTf)₂·C₆H₆ and PBu₃. [f] In the presence of 4 Å molecular sieves.

slowly at room temperature (5 d) and the diastereomeric ratio was similar to that obtained from **9a**. Regretably, the ee of the lactone **17** as determined on a HPLC (using a CHIRALCEL-ODH column) was only 25%.

Similar results were obtained with pinanediolato-allylborane reagent **11a** and the de was essentially similar to that obtained with **9a**. The ee of the lactone was only 8% at 100 °C and 10% at 25 °C. We then switched to the more reactive

(15) For a review on α-methylene-γ-butyrolactones please see: Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 110.

tartarate reagent **12a** and, as expected, the reaction was fast and the aldehyde was consumed in less than 2 d. The dr of the lactone was found to be 94:6. Again, the ee of the product was only 26%. Decreasing the reaction temperature to 0, −25, and −78 °C increased the reaction time for the allylboration, but did not improve the ee. We suspected that the low and similar ee's obtained for the allylboration products at all temperatures ranging from 25 to −78 °C could be due to the coordination of boron atom with the solvent DMF and the loss of the rigidity of the cylic six-membered transition state forcing the reaction to go through an acyclic transition state. We envisioned that changing the DMF to noncoordinating solvents might improve the ee. The reagent **12a** was generated from **4a** and CuCl or CuOTf in THF, toluene, or CH_2Cl_2. Upon addition of benzaldehyde at 0 °C, lactone **17** was obtained in good yield and in excellent de (>95% cis).[16] Unfortunately the ee values obtained were again low as in the case with DMF (Table 2). We attribute this to the limitation of the tartarate auxiliary in this type of allylboration or the interference by the copper salts present in the reaction medium.

In conclusion, we have developed a novel methodology to prepare various highly functionalized chiral and achiral allylboronate reagents via an SN_2' reaction on acetates of alcohols derived from VA or BH reaction of aldehydes. The wide range of densely functionalized allyl alcohols, which could be readily obtained via VA or BH reaction, makes this procedure very attractive for the stereoselective construction of multifunctional molecules. The allylborane reagents bearing an ester moiety have been applied for the synthesis of α-alkylidene-β-substituted-γ-butyrolactones. Further work

is in progress to improve the enantioselectivity of the lactones. We believe that these reagents will find applications in organic synthesis.

Supporting Information Available: Experimental and spectral data along with ^{1}H and ^{13}C NMR spectra for various compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **General procedure for the preparation of tartarate-based allylboronates followed by lactonization:** A mixture of CuCl or CuOTf (0.20 mmol) and PBu₃ (0.25 mmol) in toluene (2 mL) was stirred under N₂ for 15 min at 25 °C and diboron **7** (1.5 mmol) dissolved in toluene (3 mL) was added to the solution dropwise followed by the addition of allyl acetate **4a** (1.0 mmol) dissolved in toluene (1 mL). The reaction mixture was further stirred for 4 h in the case of CuOTf and for 12 h in the case of CuCl. The reaction mixture was cooled to 0 °C and benzaldehyde (0.5 mmol) was added to it and stirred at 0 °C for 2 d. The reaction mixture was then quenched with sat. NH₄Cl and extracted with ether (3 × 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under vacuum. The crude product was dissolved in CH₂Cl₂ (2 mL) and a catalytic amount of *p*TSA was added and refluxed for 5 h. The reaction mixture was quenched with sat. NaHCO₃ and extracted with CH₂Cl₂ and the combined organic layers were dried (MgSO₄) and concentrated under vacuum and purified by column chromatography (silica gel, hexanes:ethyl acetate) to obtain 74−76% yield of **17**. ^{1}H NMR (300 MHz, CDCl₃) δ (ppm) 7.37−7.29 (m, 3H), 7.16−7.13 (m, 2H), 6.30 (d, *J* = 2.85 Hz, 1H), 5.60 (d, *J* = 8.19 Hz, 1H), 5.56 (d, *J* = 2.61 Hz, 1H), 3.42 (m, 1H), 0.77 (d, *J* = 7.11 Hz, 3H); ^{13}C NMR (75 MHz, CDCl₃) δ (ppm) 170.8, 140.1, 136.4, 128.5, 128.4, 126.0, 121.8, 82.2, 38.9, 15.4; EI-MS *m/z* 188 (M)⁺, 54 [(C₄H₆)⁺, 100%]; CI-MS *m/z* 189 (M + H)⁺; HRMS-CI 189.0913 (actual), 189.0916 (calcd).

(17) Contribution No. 32 from the Herbert C. Brown Center for Borane Research.