Chen, J. L. -Y., Scott, H. K., Hesse, M. J., Willis, C. L., & Aggarwal, V. K. (2013). Highly Diastereo- and Enantioselective Allylboration of Aldehydes using alpha-Substituted Allyl/Crotyl Pinacol Boronic Esters via in Situ Generated Borinic Esters. Journal of the American Chemical Society, 135(14), 5316-5319. 10.1021/ja401564z

Highly Diastereo-and Enantioselective Allylboration of Aldehydes using α-Substituted Allyl/Crotyl Pinacol Boronic Esters via in situ Generated Borinic Esters

Jack L.-Y. Chen, Helen K. Scott, Matthew J. Hesse, Christine L. Willis and Varinder K. Aggarwal*

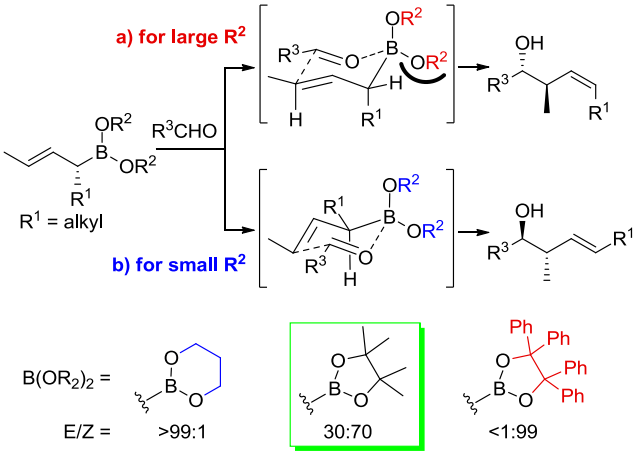
School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, United Kingdom.

Supporting Information Placeholder

ABSTRACT: Readily available, α-substituted allyl/crotyl pinacol boronic esters often give low *E*/*Z* selectivity (with *Z* favored) in reactions with aldehydes. We have found that addition of *n*BuLi to the pinacol boronic ester followed by trapping of the alkoxide with TFAA leads to an intermediate allyl borinic ester which undergoes allylboration with very high *E* selectivity. The substrate scope includes primary to tertiary alkyl α-substituents, crotyl substrates and the previously unreported β-methallyl pinacol boronic esters. The latter give very high *Z* selectivity under standard conditions which is completely reversed to high *E* selectivity under the new conditions. Monitoring the reaction by ^{11}B NMR has confirmed that the reaction proceeds through a borinic ester intermediate.

Amongst methods for making C-C bonds, asymmetric allylboration of aldehydes is one of the most reliable and important in synthesis.[1] Since Hoffmann's realization that relative stereochemistry could be controlled by the double bond geometry of crotylboronates[2] and Brown's discovery of highly enantioselective allylborations using pinane-derived reagents,[3] this reaction has established strong roots in synthesis. However, these powerful transformations are generally limited to simple allyl or crotylboron reagents; substitution in the α-position is considerably less common.[4] A complication with α-substituted allylboranes is their tendency to undergo reversible 1,3-borotropic shifts,[2b,5] which would then lead to mixtures of products.[6] A major issue of concern in reactions with α-substituted *E*-crotyl boronic esters is diastereoselectivity (or enantioselectivity with α-substituted allyl boronic esters). High *E* and *Z* selectivity can be observed with small[7,8a] and very large diols[8] attached to the boronic esters respectively, but with the much more common and much more easily accessible pinacol boronic esters, the *E*/*Z* selectivity is usually low (Scheme 1).[9] As there are a growing number of practical methods for the asymmetric synthesis of chiral allylic pinacol boronic esters,[7-10] a general solution to the low diastereoselectivity observed would be very useful. We have addressed this problem and now report a conceptually new approach, utilizing the hitherto untapped potential of chiral allylic *borinic* esters,[11] derived in situ from pinacol boronic esters.

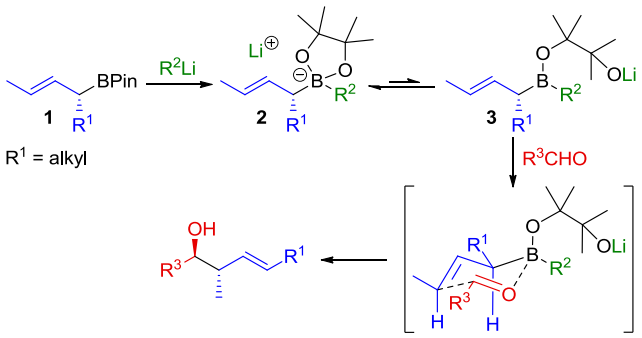
Scheme 1. Diastereoselectivity in allylboration of α-substituted boronic esters.



Design: We considered the possibility of activating an allylic boronic ester **1** with a Lewis base[12] e.g. by formation of ate complex **2** (Scheme 2). Although this may seem counter-intuitive as the boron atom is now saturated and therefore incapable of complexation with an incoming aldehyde, we reasoned that it would be in equilibrium with the ring opened and coordinately unsaturated borinic ester **3**. Although the equilibrium would lie on the side of the ate complex **2** the much higher reactivity of the borinic ester **3** was expected to channel the reaction via this intermediate. The steric environment around boron would be very different from the pinacol boronic ester and furthermore would be easily tunable by the nature of the alkyl group (R^2) added. This strategy was ultimately successful, delivering both high enantio-and diastereoselectivity in allylborations (Scheme 2).

Results: We began our studies with allyl boronic ester **4a**, which was easily prepared by lithiation-borylation.[10c,13] In a control experiment (no additives), reaction with benzaldehyde furnished a mixture of *E* and *Z* homoallylic alcohols (**5a** and **6a**) in a 25:75 ratio (Table 1, entry 1). Addition of *n*BuLi to the boronic ester followed by benzaldehyde led to a 55:45 ratio of the two alcohols, but in addition a considerable amount of the α-addition product[14] was formed (entry 2).

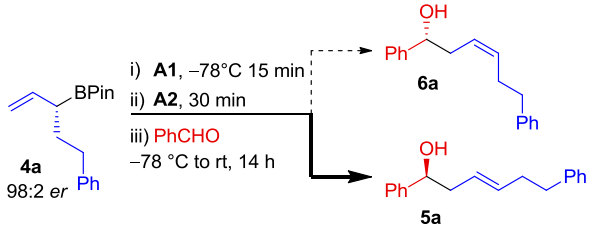
Scheme 2. Proposed new mode of reactivity via borinic ester intermediates



We reasoned that the high temperature required for the reaction (due to the low concentration of the ring opened borinic ester) resulted in a reversible 1,3-borotropic shift, leading to formation of the α product (~50:50 dr) and racemic γ product.[14] We therefore attempted to trap the intermediate borinic ester at low temperature and screened various additives, ultimately finding that acetyl chloride and TFAA were highly effective (entries 3 and 4). Not only was the high γ-selectivity, and high enantioselectivity restored, but now very high *E* selectivity (96:4 with TFAA) was also observed.

In order to compare with existing strategies, we tested Hall's conditions[10d] (entry 5) and obtained high enantioselectivity but lower diastereoselectivity. We also tested reactions of the corresponding potassium trifluoroborate salts as described by Batey[15] (entry 6) but this resulted in considerably lower diastereoselectivity.

Table 1. Optimization of allylboration

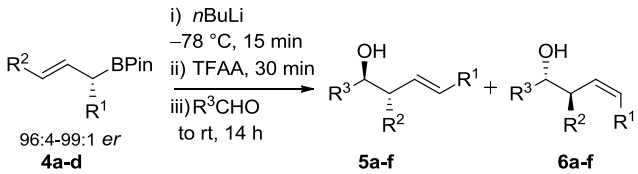


#	A1	A2	γ:α	*E*/*Z* (5:6)	Yield (5+6)	*er*
1[a]	-	-	>95:5	25:75	69	98:2
2	*n*BuLi	-	46:54	55:45	79	50:50
3	*n*BuLi	AcCl	93:7	94:6	93	98:2
4	*n*BuLi	TFAA	>95:5	96:4	84	98:2
5	$BF_3{\cdot}OEt_2$	-	>95:5	92:8	75	98:2
6[b]	$BF_3{\cdot}OEt_2$	-	>95:5	71:29	79	98:2

a) Reaction carried out at room temperature for 4 h; b) Reaction carried out on BF_3K salt of **4a**.

With optimum conditions in hand we screened a broad range of α-substituted allyl and (*E*)-crotyl pinacol boronic esters **4a-d** (prepared using our lithiation-borylation methodology[13]) with both aromatic and aliphatic aldehydes (Table 2). In varying the steric of the α-substituent R^1 a clear trend was apparent: as we increased the steric bulk from $PhCH_2CH_2$ → *i*Pr, increasing *E*-selectivity was observed (entries 2 vs. 6 and 4 vs 8). Allyl and crotyl substrates behaved similarly (entries 2 vs. 4 and 6 vs. 8) and the reactions worked just as well with both aromatic and aliphatic aldehydes (entries 8 vs. 10, 12). In every case high *E*-selectivity was observed showing the broad and general scope of the new conditions.

Table 2. Allylboration of α-substituted allyl and (*E*)-crotyl-boronic esters



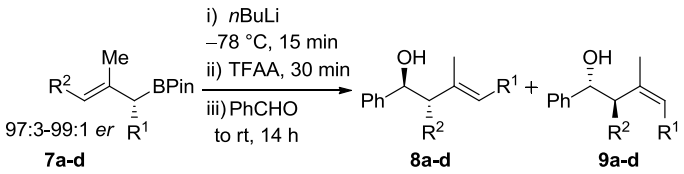
#	6	R^1	R^2	R^3	Cond	*E*/*Z* (5:6)	Yield (5+8)	er[a]
1	4a	$Ph(CH_2)_2$	H	Ph	A	25:75	74	98:2
2					B	96:4	84	98:2
3	4b	$Ph(CH_2)_2$	Me	Ph	A	26:74	72	99:1
4					B	97:3	78	98:2
5	4c	*i*Pr	H	Ph	A[b]	32:68	71	97:3
6					B	99:1	64	96:4
7	4d	*i*Pr	Me	Ph	A[b]	26:74	68	97:3
8					B	>99:1	68	95:5
9	4d	*i*Pr	Me	$Ph(CH_2)_2$	A[c]	34:66	73	97:3
10					B	99:1	88	95:5
11	4d	*i*Pr	Me	Ph_2CH	A[d]	27:73	77	96:4
12					B	>99:1	82	95:5

Conditions, A: PhCHO, rt, 14 h to 5 d; B: i) *n*BuLi, –78 °C, 15 min; ii) TFAA, 30 min; iii) R^3CHO, –78 °C to rt, 14 h. a) *er* of major product from conditions A was identical to *er* of allylic boronic ester **4**; b) reaction time = 2 d; c) reaction time = 3 d; d) reaction time = 5 d.

A very interesting set of examples emerged with *E*-crotyl pinacol boronic esters bearing a methyl group in the β-position **7a-d** (Table 3). Without additives, surprisingly high *Z* selectivity (>90:10, entries 1, 3, 5, 7) was observed, much higher than related substrates without the β-methyl group. Furthermore, using the new conditions with the additives, the high *Z* selectivity was completely over-turned and now high *E* selectivity was observed instead (>95:5, entries 2, 4, 6, 8). The allylboration of these substrates has not been previously studied[16] but we believe that the high *Z* selectivity in the absence of additives originates from enhanced $A^{1,2}$ strain in the transition state.[17]

We previously reported that allyl and methallyl boronic esters bearing chiral tertiary alkyl groups **10a-c** could be obtained with high *dr* and very high *er*.[10h] Without additives, these substrates underwent allylation reactions with PhCHO

Table 3. Allylboration of α-substituted β-methyl allyl and (*E*)-crotyl-boronic esters

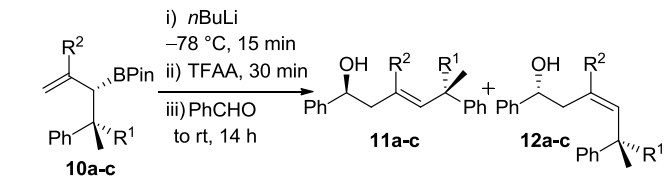


#	7	R¹	R²	Cond.	*E*/*Z* (8:9)	Yield (8+9)	*er*[a]
1	7a	Me	Me	A	10:90	88	97:3
2				B	95:5	68	97:3
3	7b	*i*Pr	Me	A	5:95	87	98:2
4				B	99:1	78	98:2
5	7c	*i*Bu	Me	A	9:91	96	97:3
6				B	97:3	77	97:3
7	7d	*i*Pr	H	A	5:95	80	99:1
8				B	97:3	72	99:1

Conditions, A: PhCHO, –78 °C to rt, 16 h to 2 d; B: i) *n*BuLi, –78 °C, 15 min; ii) TFAA, 30 min; iii) PhCHO, –78 °C to rt, 14 h. a) *er* of major product from conditions A was identical to *er* of allylic boronic ester **7**.

furnishing homoallylic alcohols bearing 1,5-stereogenic centers with high *Z* selectivity (>87:13) and very high diastereo- and enantioselectivity (Table 4, entries 1, 3, 5). Using the new Lewis base-activated conditions via the borinic ester, the high *Z* selectivity was completely over-turned, leading to the *E* isomers with high selectivity and with complete control over the 1,5-related stereocenters (entries 2, 4, 6).

Table 4. Allylboration of allyl and β-methallyl boronic esters bearing α-chiral tertiary alkyl groups



99:1 *er*, 96:4-97:3 *dr*

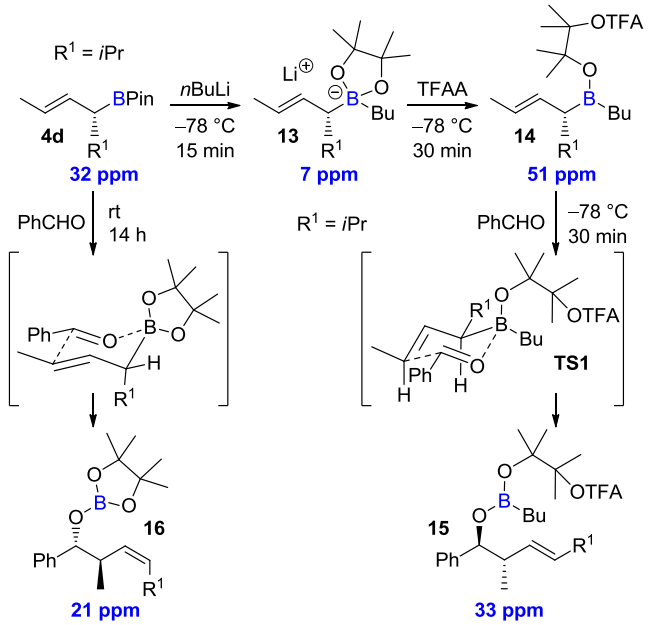
#	10	R¹	R²	Cond	*E*/*Z* (11:12)	Yield (11+12)	*er*[a]	*dr*
1	10a	Et	H	A	13:87	90	99:1	97:3
2				B	>99:1	69	99:1	97:3
3	10b	Et	Me	A	<1:99	84	99:1	97:3
4				B	>99:1	38	99:1	95:5
5	10c	Allyl	H	A	13:87	90	99:1	96:4
6				B	>99:1	76	99:1	97:3

Conditions, A: PhCHO, rt, 14 h to 5 d; B: i) *n*BuLi, –78 °C, 15 min; ii) TFAA, 30 min; iii) PhCHO, –78 °C to rt, 14 h. a) *er* of major product was identical to the *er* of the allylic boronic ester **10**.

Mechanism: Evidence for the intermediacy of a borinic ester was obtained by following the course of the allylation reaction by ^{11}B NMR. Following addition of *n*BuLi to a solution of allylic boronic ester **4d** in THF at –78 °C, a signal at 7 ppm was observed corresponding to the ate complex **13**. Following addition of TFAA, this was replaced by a new signal at 51 ppm, indicative of the formation of borinic ester **14**.[18,19] Following addition of benzaldehyde, a new signal appeared at 33 ppm, indicating the formation of boronic ester **15**. In the control experiment without additives, the boronic ester **4d** (32 ppm) was converted upon reaction with benzaldehyde to borate ester **16** (21 ppm).[20]

The relative and absolute stereochemistry of a carbamate derivative of **9b** as determined by X-ray analysis correlates with the well established 6-membered chair transition state for allylborations shown in scheme 3. The relative stereochemistry of an analogue of 11a was determined by X-ray analysis.[21] The stereochemistry at boron in **TS1** has been drawn with the O substituent axial since there is believed to be a strong anomeric effect operating through boron.[22]

Scheme 3. Identification of the reactive intermediates in both the control and Lewis base-activated allylboration reactions using ^{11}B NMR.



In summary, we have discovered a new method for activating allylic pinacol boronic esters towards allylation of aldehydes. The counter-intuitive method involves addition of *n*BuLi to the boronic ester and subsequent trapping of the alkoxide with TFAA. This generates an intermediate borinic ester which shows high reactivity and high selectivity with a range of representative aldehydes. Further explorations of the reactions of these reactive and hitherto under-utilized intermediates are on-going.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and analytical data for all compounds are available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* v. aggarwal@bristol.ac.uk.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENTS

We thank EPSRC and the European Research Council (FP7/2007-2013, ERC grant no. 246785) for financial support. M.J.H. thanks the EPSRC-funded Bristol Chemical Synthesis Doctoral Training Centre and GSK for support. We thank Dr. David Hirst (GSK) for support of the DTC project.

REFERENCES

1 First published: a) Blais, J.; L'Honoré, A.; Soulié, J.; Cadiot, P. *J. Organomet. Chem*. **1974**, *78*, 323. Reviews; b) Chemler, S. R.; Roush, W. R. Recent applications of the allylation reaction to the synthesis of natural products. *Modern Carbonyl Chemistry* Otera, J. (Ed.), Wiley-VCH, Weinheim, **2000**, pp 403-490, Chapter 11; c) Yamamoto, Y.; Asao, N. *Chem. Rev*. **1993**, *93*, 2207; d) Hoffmann, R. W.; *Pure Appl. Chem*. **1988**, *60*, 123; e) Lachance, H.; Hall, D. G. Allylboration of Carbonyl Compounds. *Organic Reactions* Denmark, S. E. (Ed.), John Wiley & Sons, New York, **2008**, *73*, 1-573; f) Kennedy, J. W. J.; Hall, D. G. Recent Advances in the preparation of allylboronates and their use in tandem reactions with carbonyl compounds. *Boronic Acids* Hall, D. G. (Ed.), Wiley-VCH, Weinheim, **2005**, pp 241-274, Chapter 6.

2 a) Hoffmann, R. W.; Zeiß, H.-J.; *Angew. Chem. Int. Ed. Engl*. **1979**, *18*, 306; b) Hoffmann, R. W.; Zeiß, H.-J. *J. Org. Chem*. **1981**, *46*, 1309; c) Hoffmann, R. W. *Pure Appl. Chem*. **1988**, *60*, 123; d) Hoffmann, R. W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem*. **1990**, *62*, 1993.

3 a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc*. **1983**, *105*, 2092; b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc*. **1986**, *108*, 293; c) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.

4 The 2008 comprehensive review of allylation reaction using allylboron reagents by D. G. Hall(1e) cites 49 pages of tabulated individual reactions using an α-substituted allylboron reagents compared to 419 pages of reactions using allylboron reagents without α-substitution.

5 a) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem*. **1977**, *132*, 9; b) Bubnov, Y. N.; Gurskii, M. E.; Gridnev, I. D.; Ignatenko, A. V.; Ustynyuk, Y. A.; Mstislavsky, V. I. *J. Organomet. Chem*. **1992**, *424*, 127.

6 In certain cases this can be controlled: a) Hancock, K. G.; Kramer, J. D. *J. Am. Chem. Soc*. **1973**, 6463; b) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc*. **2009**, *131*, 14602; c) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc*. **2009**, *131*, 14174; d) Gonzalez, A. Z.; Roman, J. G.; Alicea, E.; Canales, E.; Soderquist, J. A. *J. Am. Chem. Soc*. **2009**, *131*, 1269; e) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2007**, *46*, 359; f) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc*. **1985**, *107*, 2564.

7 Althaus, M.; Mahmood, A.; Suarez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2010**, *132*, 4025.

8 a) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc*. **2002**, *124*, 13644; b) Pietruszka, J.; Schöne, N. *Eur. J. Org. Chem*. **2004**, 5011; c) Pietruszka, J.; Schöne, N. *Synthesis* **2006**, 24; d) Cmrecki, V.; Eichenauer, N. C.; Frey, W.; Pietruszka, J. *Tetrahedron* **2010**, *66*, 6550.

9 a) Hoffmann, R. W.; Weidmann, U. *J. Organomet. Chem*. **1980**, *195*, 137; b) Andersen, M. W.; Hildebrandt, B.; Kosher, G.; Hoffmann, R. W. *Chem. Ber*. **1989**, *122*, 1777; c) Carosi, L.; Lachance, H.; Hall, D. G.; *Tetrahedron Lett*. **2005**, *46*, 8981; In certain specific cases, the use of Lewis acids has provided high *E* selectivity for α-alkyl substituted pinacol boronic esters: c) Peng, F.; Hall, D. G.; *Tetrahedron Lett*. **2007**, *48*, 3305; d) Peng, F.; Hall, D. G. *J. Am. Chem. Soc*. **2007**, *129*, 3070; e) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc*. **2007**, *129*, 14856; f) Chen, M.; Roush, W. R. *Org. Lett*. **2010**, *12*, 2706.

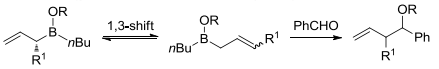
10 a) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc*. **1980**, *102*, 7590; b) Pelz, N. F.; Woodward, A. R.; Burks, H. E. Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc*. **2004**, *126*, 16328; c) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, 2275; d) Carosi, L.; Hall, D. G. *Angew. Chem. Int. Ed*. **2007**, *46*, 5913; e) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 10634; f) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc*. **2011**, *133*, 2410; g) Pulis, A.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2012**, *135*, 7570; h) Sonawane, R. P.; Jheengut, V.; Larouche-Gauthier, R.; Rampalakos, K.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2011**, 50, 3760; i) Posseme, F.; Deligny, M.; Carreaux, F.; Carboni, B. *J. Org. Chem*. **2007**, *72*, 984; j) Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem. Int. Ed*. **2012**, *51*, 521.

11 a) Midland, M. M.; Preston, S. B. *J. Am. Chem. Soc*. **1982**, *104*, 2330; b) Brown, H. C.; Jayaraman, S. *J. Org. Chem*. **1993**, *58*, 6791. The generality and scope of these methods is either limited by the method of generation of the borinic acid (ref. 10a) or is non-selective (ref 10b).

12 Denmark, S. E.; Beutner, G. L.; *Angew. Chem. Int. Ed*. **2008**, *47*, 1560.

13 a) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2007**, *46*, 7491; b) Webster, M. P.; Partridge, B. M.; Aggarwal, V. K. *Org. Synth*. **2011**, *88*, 247. c) Larouche-Gauthier, R.; Fletcher, C. J.; Couto, I.; Aggarwal, V. K. *Chem. Commun*. **2011**, *47*, 12592; d) Zschage, O.; Hoppe, D. *Angew. Chem. Int. Ed*. **1989**, *28*, 69.

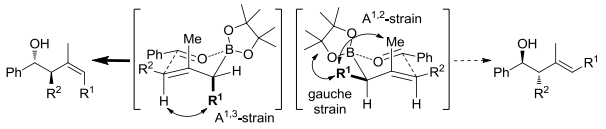
14 The α-products (1:1 mixture of diastereomers) originate from 1,3-borotropic shift followed by allylation:



15 a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett*. **1990**, *40*, 4289; b) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Synthesis* **2000**, 990.

16 There is a single report by Morken describing allylboration of related β-boryl α-substituted pinacol boronic esters where high *Z* selectivity was also observed: Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett*. **2005**, *7*, 5505.

17 Protodeboronation of these substrates also led to high *Z* selectivity (>95:5). Both allylboration and protodeboronation are believed to occur through similar transition states. For a discussion see: Hesse, M. J.; Butts, C. P.; Willis, C. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2012**, *51*, 12444. The high *Z*-selectivity observed is due to (dominant) gauche interactions of the α-substituent with the pinacol ester together with enhanced A1,2-strain associated with methallyl boronic esters:



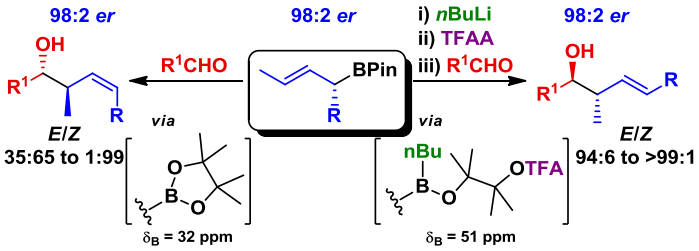
18 Chemical shift in accordance with borinic esters found in literature: Cole, T. E.; Haly, B. D. *Organometallics* **1992**, *11*, 652.

19 ^{11}B NMR has also been used to analyse the intermediates formed when AcCl or CCl3COCl is used as the additive (in place of TFAA) in the allylation. In both cases, ^{11}B NMR analysis of the intermediate formed showed a signal at ~51 ppm. The fact that the use of all three additives result in the formation of intermediates with similar signals in the ^{11}B NMR indicates that the intermediate is a pinacolate-derived borinic ester (partially ring-opened), and not an intermediate with complete displacement of the pinacolate by the acid derivative (TFA^-/Cl^-). We thank one of the reviewers for providing this suggestion.

20 Chemical shifts in accordance with those found in the literature: Cole, T. E. 11B NMR Chemical Shifts; http://www.chemistry.sdsu.edu/research/BNMR/ and references therin; (accessed: 18/12/2012).

21 See Supporting Information.

22 Shiner, C. S.; Garner, C. M.; Haltiwanger, R. C. *J. Am. Chem. Soc*. **1985**, *107*, 7167.


98:2 er
OH
R1
R
E/Z
35:65 to 1:99
R1CHO
via
δB = 32 ppm
98:2 er
BPin
R
i) nBuLi
ii) TFAA
iii) R1CHO
via
nBu
OTFA
δB = 51 ppm
98:2 er
OH
R1
R
E/Z
94:6 to >99:1