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

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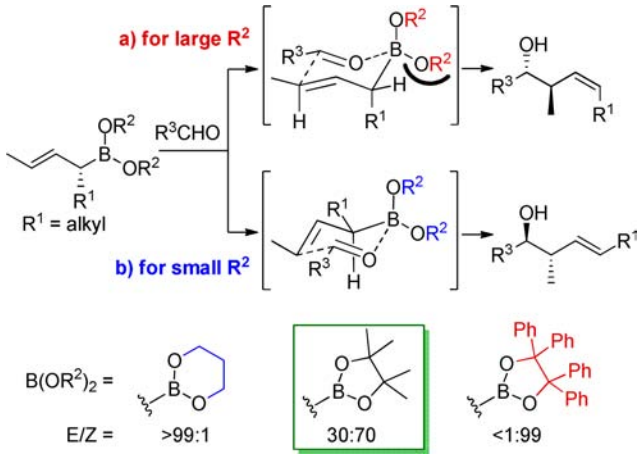
Supporting Information

ABSTRACT: Readily available, α-substituted allyl/crotyl pinacol boronic esters often give low *E*/*Z* selectivity (with *Z* favored) in reactions with aldehydes. We 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 confirmed that the reaction proceeds through a borinic ester intermediate.

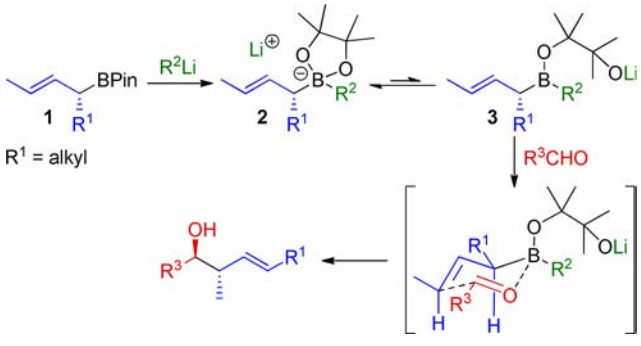
Among methods for making C−C bonds, asymmetric allylboration of aldehydes is one of the most reliable and important in synthesis.[1] Since Hoffmann's realization that relative stereochemistry could be controlled by the double-bond geometry of crotylboronates[2] and Brown's discovery of highly enantioselective 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 more common and 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 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.

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 counterintuitive as the boron atom is now saturated and thus 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,

Scheme 1. Diastereoselectivity in Allylboration of α-Substituted Boronic Esters



Scheme 2. Proposed New Mode of Reactivity via Borinic Ester Intermediates



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delivering both high enantio- and diastereoselectivity in allylborations (Scheme 2).

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**, **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).

We reasoned that the high temperature required for the reaction (due to 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 α 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, 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.

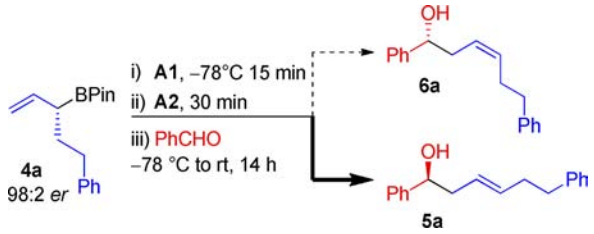
In order to compare with existing strategies, we tested Hall's conditions[10d] (entry 5) and obtained high enantioselectivity but lower diastereoselectivity. We also tested reactions of the corresponding potassium trifluoroborate salts as described by Batey[15] (entry 6), but this resulted in considerably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

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 sterics 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; 4 vs 8). Allyl and crotyl substrates behaved similarly (entries 2 vs 4; 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.

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 overturned, 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 furnishing homoallylic alcohols bearing 1,5-stereogenic centers

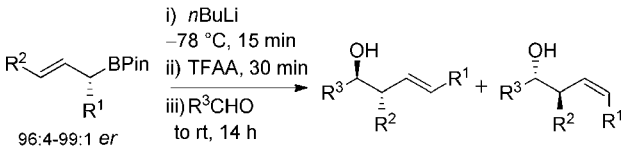
Table 1. Optimization of Allylboration



no.	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 rt for 4 h. [b]Reaction carried out on BF_3K salt of **4a**.

Table 2. Allylboration of α-Substituted Allyl and (*E*)-Crotyl-boronic Esters



no.	6	R^1	R^2	R^3	cond.[a]	*E*/*Z* (5:6)	yield (5+6)	er[b]
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[c]	32:68	71	97:3
6					B	99:1	64	96:4
7	**4d**	*i*Pr	Me	Ph	A[c]	26:74	68	97:3
8					B	>99:1	68	95:5
9	**4d**	*i*Pr	Me	$Ph(CH_2)_2$	A[d]	34:66	73	97:3
10					B	99:1	88	95:5
11	**4d**	*i*Pr	Me	Ph_2CH	A[e]	27:73	77	96:4
12					B	>99:1	82	95:5

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

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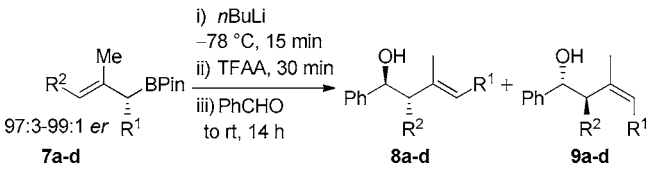
Table 3. Allylboration of α-Substituted β-Methyl Allyl and (*E*)-Crotyl-boronic Esters

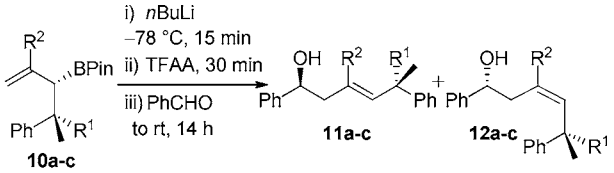


no.	7	R^1	R^2	cond.[a]	*E*/*Z* (8:9)	yield (8+9)	er[b]
1	**7a**	Me	Me	A	10:90	88	97:3
2				B	95:5	68	97:3
3	**7b**	*i*Pr	Me	A	5:95	87	98:2
4				B	99:1	78	98:2
5	**7c**	*i*Bu	Me	A	9:91	96	97:3
6				B	97:3	77	97:3
7	**7d**	*i*Pr	H	A	5:95	80	99:1
8				B	97:3	72	99:1

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

with high *Z* selectivity (>87:13) and very high diastereo- and enantioselectivity (Table 4, entries 1, 3, 5). Using the new

Table 4. Allylboration of Allyl and β-Methallyl Boronic Esters Bearing α-Chiral Tertiary Alkyl Groups



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

no.	10	R^1	R^2	cond.[a]	*E*/*Z* (11:12)	yield (11+12)	er[b]	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

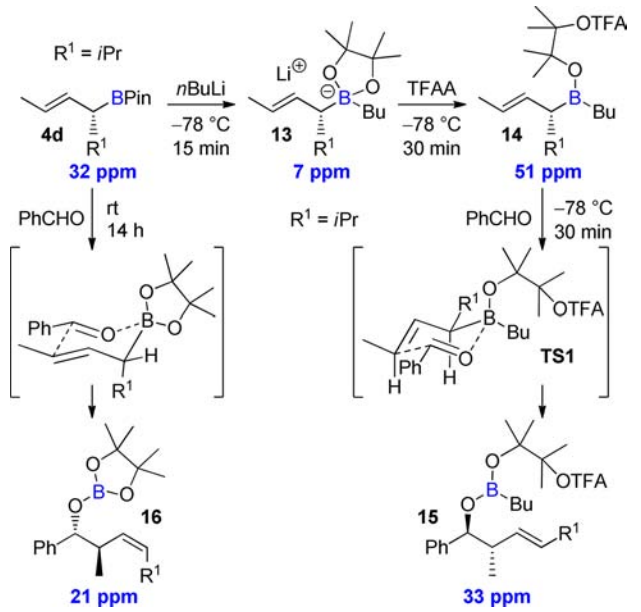
[a]Conditions, A: PhCHO, THF, rt, 14 h to 5 d; B: (i) THF, *n*BuLi, −78 °C, 15 min; (ii) TFAA, 30 min; (iii) PhCHO, −78 °C to rt, 14 h. [b]*er* of major product was identical to the *er* of the allylic boronic ester **10**.

Lewis base-activated conditions via borinic ester intermediates, the high *Z* selectivity was completely overturned, leading to the *E* isomers with high selectivity and with complete control over the 1,5-related stereocenters (entries 2, 4, 6).

Evidence for the intermediacy of a borinic ester was obtained by following the course of the allylation reaction by ^{11}B NMR. After 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 subsequent addition of TFAA, this was replaced by a new signal at 51 ppm, indicative of the formation of borinic ester **14**.[18,19] Addition of benzaldehyde, led to 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 **8b** was determined by X-ray analysis and correlates with the well established six-membered chair transition state for allylborations shown in Scheme 3. The relative stereochemistry

Scheme 3. Identification of the Reactive Intermediates in Both the Control and Lewis Base-Activated Allylboration Reactions Using ^{11}B NMR



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]

In summary, we have discovered a new method for activating allylic pinacol boronic esters toward allylation of aldehydes. The counterintuitive 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 selectivity with a range of representative aldehydes. Further explorations of the reactions of these reactive and hitherto under-utilized intermediates are ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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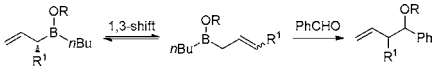
(14) The α-products (1:1 mixture of diastereomers) originate from 1,3-borotropic shift followed by allylation:



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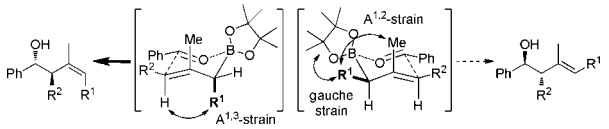
(17) Protodeboronation of these substrates also led to high *Z* selectivity (>95:5). Both allylboration and protodeboronation are believed to occur through similar transition states. For a discussion see: Hesse, M. J.; Butts, C. P.; Willis, C. L.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12444 . 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: .



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(19) ^{11}B NMR has also been used to analyse the intermediates formed when AcCl or CCl_3COCl 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 therein (accessed December 18, 2012).

(21) See SI for details.

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