E/Z-Alkene Synthesis

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Diastereodivergent Synthesis of Trisubstituted Alkenes through Protodeboronation of Allylic Boronic Esters: Application to the Synthesis of the Californian Red Scale Beetle Pheromone**

Matthew J. Hesse, Craig P. Butts, Christine L. Willis, and Varinder K. Aggarwal**

Trisubstituted alkenes are ubiquitous structures in natural products, and particularly prevalent in the wide range of polyketide- and terpene-derived natural products (Figure 1).

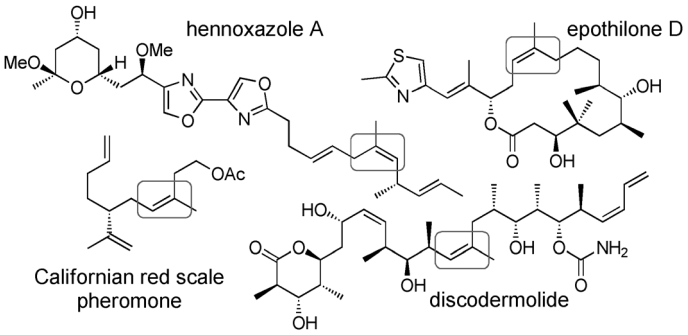
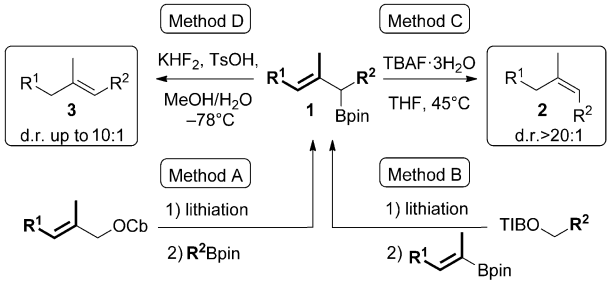


Figure 1. Natural products containing *Z*-trisubstituted olefins.

In synthesis, these motifs are often focal points around which disconnections are made. As such, methods for the synthesis of alkenes in stereochemically defined forms are of central importance. A number of methods have been developed for the selective synthesis of either *E*- or *Z*-trisubstituted alkenes,[1] based on carbonyl addition reactions,[2–4] alkyne functionalization,[5] or metathesis.[6]

Generally, there are more methods for the selective synthesis of trisubstituted *E*-alkenes (e.g., Wittig reaction, metathesis) than for their *Z*-counterparts. It would therefore be useful if one could transform easily available trisubstituted *E*-alkenes into the more difficult to access *Z*-isomers, particularly if the *E*-alkenes themselves were derived through a convergent assembly (Scheme 1). Herein, we report the protodeboronation and conversion of *E*-allylic boronic esters **1** into *Z*-trisubstituted alkenes **2** with d.r. > 20:1. Furthermore, we have been able to alter the reaction pathway during protodeboronation and target the rearranged *E*-alkenes **3** instead.



Scheme 1. Synthesis and diastereodivergent protodeboronation of allylic boronic ester **1**. CbO = *N*,*N*′-diisopropylcarbamate, TIBO = 2,4,6-triisopropylbenzoate, Bpin = pinacolatoboron.

We have previously reported that the reactions of lithiated carbamates with boronic esters provide a useful method for the stereoselective, reagent-controlled homologation of boronic esters,[7] a reaction that can be conducted iteratively, and in one pot, to rapidly form complex molecules.[8] In the context of a total synthesis program, we recognized the potential of using the lithiation–borylation reaction in the convergent assembly of two complex moieties (Scheme 1, methods A and B). If the product of such a coupling was an allylic boronic ester **1**, then simple protodeboronation would provide an opportunity to remove the boron atom, and would also give a trisubstituted alkene. However, such a strategy has not been utilized previously and despite the simplicity of the protodeboronation process, no information concerning the geometry of the resulting alkene that would be formed had been reported.[9]

We began our studies of the key protodeboronation reaction on a representative allylic boronic ester **4a** using conditions that we had reported for protodeboronation of tertiary benzylic boronic esters: TBAF·3 H_2O in THF[10] (Table 1, entry 1). These conditions were highly effective but, surprisingly, gave exclusively the *Z*-alkene **5a** (> 20:1) as determined by nOe spectroscopy. Acetic acid could also be employed; it required higher temperatures and gave lower selectivity, but still in favor of the *Z*-isomer (Table 1, entry 3). CsF with 1.1 equivalents of H_2O was not effective, returning mostly starting material. We were keen to explore alternative substituents on boron, and conversion to the trifluoroborate salt[11] resulted in spontaneous protodeboronation, which gave the *E*-alkene **6a** predominantly (Table 1, entry 5).[12] The selectivity could be increased by lowering the temperature

[*] M. J. Hesse, Dr. C. P. Butts, Prof. C. L. Willis, Prof. V. K. Aggarwal
School of Chemistry, University of Bristol
Cantock's Close, Bristol, BS8 1TS (UK)
E-mail: chris.willis@bristol.ac.uk
v.aggarwal@bristol.ac.uk

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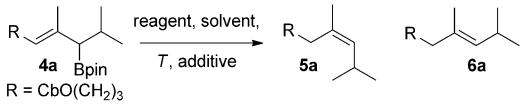
Table 1: Screening of conditions for protodeboronation of allylic boronic ester **4**.



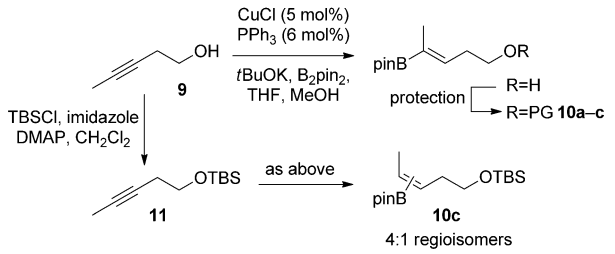
Ent.	Reagent	Solvent	*T* [°C]	Add.	**5a**:**6a**[a]	Yield [%][b]
1	TBAF·3 H_2O[c]	THF	45	–	>20:1	quant.
2	AcOH	neat	80	–	n.d.	42
3	AcOH	neat	120	–	5:1	85
4	CsF,[d] H_2O[e]	THF	45	–	–	trace
5	KHF_2[f]	MeOH/H_2O[g]	23	–	1:4	95
6	KHF_2[f]	MeOH/H_2O[g]	0	–	1:5	96
7	KHF_2[f]	MeOH/H_2O[g]	−30	TsOH[h]	1:7.5	94
8	KHF_2[f]	MeOH/H_2O[g]	−78	TsOH[h]	1:9	96

[a] Ratio determined by ^{1}H NMR spectroscopy, geometry determined by nOe spectroscopy. [b] Yields of isolated products. [c] 2 equiv. [d] 1.5 equiv. [e] 1.1 equiv. [f] 4 equiv. [g] 9:1 mixture by volume. [h] 5 equiv. n.d. = not determined.

(Table 1, entry 6), but required the addition of an acid,[13] and ultimately led to high *E*-selectivities (Table 1, entries 7 and 8).

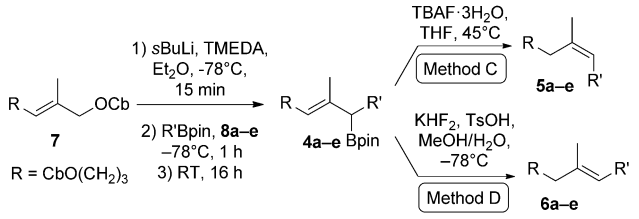
With two different methods that gave *Z*- or *E*-alkene isomers selectively (Scheme 1, methods C and D), the scope of the new protodeboronation process was explored with a range of allylic boronic esters (Table 2). The first set of substrates was prepared by method A (Scheme 1), the reaction of a lithiated allylic carbamate[14] with boronic esters **8a–e**. *E*-Allylic carbamate **7** was prepared through a cross-metathesis/reduction route.[15] Treatment of the allylic boronic ester substrates **4a–e** with TBAF led to trisubstituted *Z*-alkenes **5a–e** with uniformly high *Z*-selectivity (Table 2, entries 1–5). Remarkably, even with a very sterically hindered substrate (R = *t*Bu; Table 2, entry 4) complete *Z*-selectivity was still observed. In the case of R = Ph, milder conditions had to be employed because of the competing formation of α-protodeboronation side products (Table 2, entry 5).[16] The process for formation of the *E*-alkenes **6a–e** was less selective but nevertheless, synthetically useful levels of selectivity were observed in most cases (Table 2, entries 1, 3, and 4).

In order to probe the functional-group tolerance of the methodology, a variety of hydroxy-protected vinyl boronic esters **10a–c** were prepared and reacted using method B (Scheme 1). The *Z*-vinyl boronic esters were prepared by a Cu^I-catalyzed formal "hydroboration" of hydroxy alkyne **9** (Scheme 2).[17] It should be noted that protection of the hydroxyalkyne as silyl ether **11** prior to "hydroboration" resulted in lower regioselectivity.



Scheme 2. Cu-catalyzed hydroboration of internal alkynes. PG = protecting group.

Table 2: Diastereodivergent protodeboronation of allylic boronic esters **8a–e**.



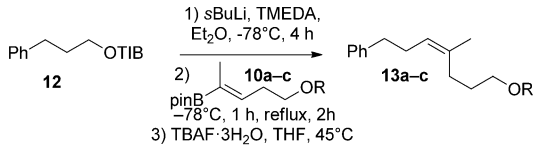
Ent.	Boronic Ester **8** R′	Method C Yield of **4** [%][a]	Yield of **5** [%]	*Z*:*E*[b]	Method D Yield of **6** [%]	*Z*:*E*[b]
1	**8a** *i*Pr	82	98	>20:1	95	1:9
2	**8b** 	76	99	>20:1	97	1:2
3	**8c** 	78	99	>20:1	93	1:8
4	**8d** *t*Bu	70	98	>20:1	99	1:10
5	**8e** Ph	73	95[c]	>20:1	92	1:1

[a] Yields of isolated products. [b] Ratio determined by ^{1}H NMR spectroscopy, geometry determined by nOe spectroscopy. [c] Obtained as a 4.5:1 mixture of γ/α isomers using CsF (1.5 equiv) and H_2O (1.1 equiv) in pentane at RT for 16 h.

Lithiation of TIB ester **12** (which was found to be superior to carbamates in reactions with boronic esters bearing an adjacent sp^2 carbon atom),[18] and subsequent reaction with the *Z*-vinyl boronic esters **10a–c** was followed by protodeboronation with TBAF to give the *Z*-trisubstituted alkenes **13a–c** in good yield and high d.r. (although the latter was slightly reduced; Table 3). This result indicated that carbamates (Table 2), acetals, and ethers are all tolerated by the reaction. Silyl groups were cleaved under the reaction conditions, giving the corresponding deprotected and protodeboronated product **13c** in good yield.

Our mechanistic model for the observed high *Z*-selectivity is based on analogous reactions of α-substituted allyl boronic

Table 3: Lithiation–borylation–protodeboronation of functionalized substrates.



Entry	Substrate	R	Product	Yield [%][a]	*Z*:*E* ratio[b]
1	**10a**	THP	**13a**	68	13:1
2	**10b**	Bn	**13b**	77	14:1
3	**10c**	TBS	**13c**	74[c]	20:1

[a] Yields of isolated products. [b] Determined by ^{1}H NMR spectroscopy, geometry determined by nOe spectroscopy. [c] Product obtained as the deprotected alcohol.

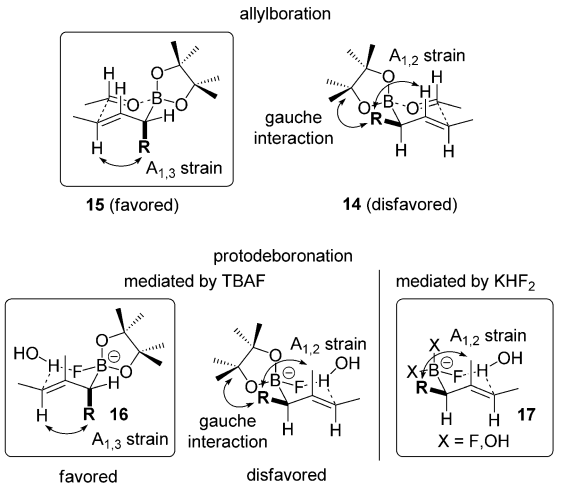


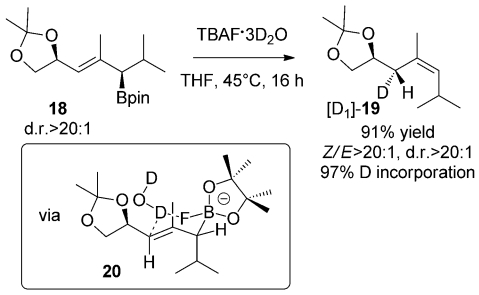
Figure 2. Proposed transition states for transformations of α-substituted allylic boronates.

esters with aldehydes (Figure 2).[19] In these systems, low to moderate *Z*-selectivity is observed with pinacol esters. The outcome of such allylboration has been rationalized on the basis of competing steric interactions. When the α-substituent, R, is in an equatorial position in the six-membered-chair transition state (TS) **14** (leading to the *E*-isomer), it suffers from severe gauche interactions with the bulky pinacol group and minor $A_{1,2}$ strain with the vinylic substituent (usually a proton). In contrast, when the substituent is in an axial position (as in **15**, leading to the *Z*-isomer), it only suffers from $A_{1,3}$ strain. The *Z*-selectivity observed is indicative that the gauche interactions with the bulky pinacol ester are much greater than the $A_{1,3}$ strain.

We propose that the *Z*-selective protodeboronation proceeds through a similar six-membered TS, **16**, whereby fluoride both activates the boronic ester as the "ate" complex and directs addition of water to the γ-position. The enhanced *Z*-selectivity observed in protodeboronation over allylboration of aldehydes is likely to be a consequence of the enhanced $A_{1,2}$ strain between the R group and the methyl substituent in addition to the factors described above.

When the pinacol ester is exchanged for the less bulky trifluoroborate salt (or, upon hydrolysis, the boronic acid) the balance of steric forces is altered such that $A_{1,3}$ strain now constitutes the dominant factor. The reaction now proceeds through TS **17**, in which the α-substituent is in a pseudoequatorial position, leading to the *E*-product. The lower selectivities observed in this reaction can be attributed to the more balanced steric demands of the system. The acid-catalyzed reactions mirror the sense and degree of selectivity that can be observed in TFA-mediated protonation of similarly substituted allyl silanes.[20]

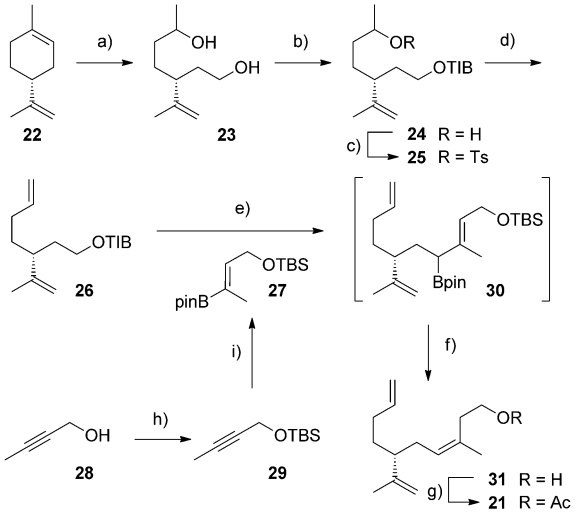
In order to determine whether protonation occurs supra- or antarafacially, a diastereomerically pure allylic boronic ester **18** was prepared.[21] Subsequent treatment with TBAF·3 D_2O gave a single diastereomer of the deuterated product [D_1]-**19** (Scheme 3), the stereochemistry of which was determined by quantitative nOe distance analysis (see the



Scheme 3. Deuterodeboronation of **18**.

Supporting Information).[22] The spectra showed that suprafacial incorporation of deuterium had occurred, which is consistent with our proposed cyclic TS **20**.[23]

In order to further demonstrate the utility of this methodology, a synthesis of a component (**21**,[24] Scheme 4) of the sex



Scheme 4. Total synthesis of a component of the sex pheromone of the Californian red scale insect. a) 1) O_3, MeOH, −78 °C; 2) $NaBH_4$, MeOH, 0 °C, 82% over 2 steps; b) NaH, THF, 0 °C, then TIBCl, reflux, 48 h, 86%; c) TsCl, Et_3N, DMAP, CH_2Cl_2, 93%; d) *t*BuOK, hexane, RT, 96% (regioselectivity = 14:1); e) *s*BuLi, TMEDA, Et_2O, −78 °C, 4 h, then **27**, −78 °C, 1 h, heating to reflux, 2 h; f) TBAF·3 H_2O, THF, RT, 2 h, then 45 °C, 16 h, 73% over 2 steps (d.r. > 95:5); g) Ac_2O, pyridine, RT, 1.5 h, 99%; h) TBSCl, imidazole, DMAP, CH_2Cl_2, RT, 99%; i) CuCl (5 mol%), PPh_3 (6 mol%), *t*BuOK (20 mol%), B_2pin_2, MeOH, THF, RT, 16 h, 88% (d.r. > 95:5). DMAP = 4-dimethylaminopyridine, TBAF·3 H_2O = tetra-*n*-butylammonium fluoride trihydrate, TBSCl = *tert*-butyldimethylsilyl chloride, TIBCl = 2,4,6-triisopropylbenzoyl chloride, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylene diamine.

pheromone of the Californian red scale beetle, *Aonidiella aurantii*, was undertaken. The Californian red scale beetle is a major citrus crop pest found in many areas of the world; and as such, **21** is used in pest control[25] by acting as an attractant to the mobile male members of the species. This compound has been previously synthesized on several occasions,[26] and often acts as a benchmark for the effectiveness of *Z*-selective trisubstituted olefination methodologies. We believed that the

target compound could be easily obtained using our lithiation–borylation–protodeboronation methodology.

Our synthesis began with regioselective ozonolysis of (*R*)-limonene **22**;[27] reductive workup gave diol **23** in excellent yield in a process that could be performed on a multi-gram scale. In order to install the required terminal alkene, we initially selectively functionalized the primary hydroxy group using the bulky TIB chloride, which gave the benzoate **24** in good yield and complete chemoselectivity. This result enabled us to differentiate the two alcohols, and also to set up the primary alcohol for a lithiation–borylation reaction. Activation of the remaining secondary alcohol as the tosylate **25** followed by elimination using *t*BuOK in hexane gave the required alkene **26** with a high degree of regioselectivity (14:1).[28] During a solvent screen for this reaction, we observed that nonpolar solvents gave the best selectivity, despite the low solubility of the base.

With the benzoate portion of the molecule in hand, we turned our attention to the vinyl boronic ester **27**. Propargylic alcohol **28** was protected as the TBS ether **29** and then subjected to a Cu^{I}-catalyzed formal hydroboration reaction, which occurred with essentially complete regioselectivity (in contrast, a 4:1 mixture of products was obtained in the hydroboration of homolog **11** (see Scheme 2)). Deprotonation of the TIB ester **26** followed by addition of the boronic ester **27** gave an intermediate ate complex, which underwent 1,2-metallate rearrangement upon heating to give the allylic boronic ester **30**.[29] The crude material was then treated with TBAF·3 H_2O, initially at room temperature to effect deprotection of the silyl ether before warming to 45 °C to promote protodeboronation. Following purification, homoallylic alcohol **31** was obtained in 73 % yield from **27**, with more than 20:1 *Z*/*E* selectivity. Interestingly, competing elimination of the TBS ether was not observed during the course of this reaction sequence. Finally, acetylation furnished the natural product **21** in 46 % overall yield starting from commercially available (−)-limonene in what constitutes the most concise and efficient synthesis of **21** to date.

In conclusion, we have found that *E*-allylic boronic esters undergo a highly selective protodeboronation with TBAF·3 H_2O to give *Z*-trisubstiuted alkenes with high selectivity. By simply changing the conditions to KHF_2/TsOH, the selectivity is switched to give predominantly the *E*-alkene instead. The synthetic utility of the methodology has been illustrated using a short synthesis of the sex pheromone **21**. This latter synthesis demonstrates the application of the methodology, and also shows the power of the lithiation–borylation–protodeboronation sequence for the convergent and stereoselective construction of relatively complex molecules.

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Keywords: alkenes · allylic compounds · diastereoselectivity · natural products · protodeboronation

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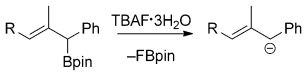
[16] The α-protodeboronation product is believed to arise from a pathway involving a discrete doubly stabilized anion, which is then protonated at the α-position.



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