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Vinylidene Homologation of Boronic Esters and its Application to
the Synthesis of the Proposed Structure of Machillene

James M. Fordham,[a] Matthew N. Grayson*[b] and Varinder K. Aggarwal*[a]

Abstract: Alkenyl boronic esters are important reagents in organic synthesis. Herein, we report that these valuable products can be accessed by the homologation of boronic esters with lithiated epoxysilanes. Aliphatic and electron-rich aromatic boronic esters provided vinylidene boronic esters in moderate to high yields, while electron-deficient aromatic and vinyl boronic esters were found to give the corresponding vinyl silane products. Through DFT calculations, this divergence in mechanistic pathway has been rationalized by considering the stabilization of negative charge in the C-Si and C-B bond breaking transition states. This vinylidene homologation was used in a short six step stereoselective synthesis of the proposed structure of machillene, however, synthetic and reported data were found to be inconsistent.

Vinyl boronic esters are versatile intermediates in organic chemistry, participating in a range of transformations including cross-coupling,[1] oxidation,[2] homologation[3] and many others.[4] Due to their synthetic utility, new methodologies that expand the range of accessible vinyl boronic esters are highly desirable, especially those that enable the introduction of sp²-rich motifs. Many precursors have been used to prepare vinyl boronic esters including alkenes,[5] vinyl halides,[6] alkenes,[7] carboxylic acids,[8] aldehydes,[9] ketones[10] and, recently, boronic esters themselves. Through modification of their conjunctive cross-coupling methodology,[11] Morken and co-workers were able to achieve the vinylidenation of organoboronic esters 1 to prepare a range of 1,1-disubstituted vinyl boronic ester 3 (Figure 1).[12] As sp²-rich organoboronic esters are readily available,[13-15] vinylidene homologations have the potential to greatly expand the range of available vinyl boronic esters. Furthermore, we envisaged a process wherein iterative homologation of a boronic ester could be interrupted by a vinylidenation protocol to create more diverse polyketide-type structures.[16]

Inspired by our previous work on the reaction of lithiated epoxides with boronic esters,[17] we set out to exploit the reaction of lithiated epoxysilane 4 with boronic esters 1 in a novel vinylidene homologation (Figure 1). We postulated that after formation of a boron-ate complex, 1,2-metallate rearrangement would occur to give β-alkoxy-α-silyl boronic ester intermediate 5, which could undergo a Peterson-type elimination[18] to give vinyl boronic ester 3. If successful, this method would serve as a transition-metal free alternative to the procedure of Morken. Based on previous reports,[19] we anticipated that the desired Peterson elimination pathway would be favoured over the alternative boron-Wittig reaction (forming vinyl silane 6),[20] although the mechanistic rationale for this outcome remained unclear.

Encouraged by this precedent, we reacted phenethyl boronic ester 1a with lithiated epoxysilane 4a (Table 1).[21] After stirring at 40 °C for 1 h, 1H NMR analysis of the reaction mixture indicated that full 1,2-migration had occurred and, after chromatographic purification, vinyl boronic ester 3a was obtained as the exclusive product in 77% yield (see S.I. for optimisation). The methodology was found to be compatible with more sterically hindered secondary and tertiary boronic esters (products 3b and 3c), although the latter case required higher stoichiometry of 4 for optimum yield. Boronic esters containing base and nucleophile-sensitive groups were also employed and the corresponding homologated products 3d and 3e were obtained in 49% and 38% yield, respectively. We were eager to investigate more elaborate and pharmacologically relevant boronic esters. Thus, cyclobutyl and azetidinyl substrates were subjected to the vinylidenation reaction and gave the corresponding products 3f and 3g in 72% and 55% yield, respectively, the former being obtained with complete diastereospecificity (d.s.). The sensitive vinyl cyclopropyl boronic ester 3h was isolated in 51% yield (75% NMR yield). Sterically hindered menthyl and cholesteryl-derived boronic esters gave vinylidene products 3i and 3j in lower yield (32% and 46%, respectively) with a small amount of over-homologation apparent. A polyketide-type substrate was also subjected to the reaction conditions, giving the desired product 3k.

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in 47% yield. This substrate is notable considering the potential for β-elimination via intermediate B, which was not observed under our reaction conditions.\(^{[20]}\) As lithiated epoxysilanes are configurationally stable at low temperature,\(^{[21]}\) we expected that a trans-substituted epoxysilane would furnish the trisubstituted (E)-olefin with high selectivity via intermediate Siii (Table 1B). Indeed, epoxysilanes 7b and 7c\(^{[22]}\) gave the corresponding products 3l and 3m in 30% and 73% yield respectively and as a single isomer.

### Table 1. Vinylidene homologation of aliphatic boronic esters.

<table>
<thead>
<tr>
<th>R</th>
<th>7a Yield</th>
<th>8 Yield</th>
<th>3a Yield</th>
<th>3b Yield</th>
<th>3c Yield</th>
<th>3e Yield</th>
<th>3f Yield</th>
<th>3g Yield</th>
<th>3h Yield</th>
<th>3i Yield</th>
<th>3j Yield</th>
</tr>
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<tbody>
<tr>
<td>H</td>
<td>74%</td>
<td>34%</td>
<td>77%</td>
<td>58%</td>
<td>35%</td>
<td>31%</td>
<td>39%</td>
<td>47%</td>
<td>51%</td>
<td>31%</td>
<td>100%</td>
</tr>
<tr>
<td>Bn</td>
<td>67%</td>
<td>55%</td>
<td>68%</td>
<td>77%</td>
<td>51% (75%)</td>
<td>100% d.a.</td>
<td>62%</td>
<td>55%</td>
<td>51% (75%)</td>
<td>100% d.a.</td>
<td></td>
</tr>
<tr>
<td>TMS</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
<td></td>
</tr>
</tbody>
</table>

DFT calculations were performed to better understand the factors that determined the outcome of the elimination pathway. All calculations were performed with Gaussian 16\(^{[23]}\) at the B3LYP-D3(BJ)/6-311G(d,p)-IEFPCM(n-pentane)//B3LYP/6-31G(d) level of theory (see S.I. for computational details). Previous computational studies of organic reactions with similar methods provided results in accord with experiment.\(^{[24-26]}\)

The thermodynamically favoured product was calculated to be the vinyl silane by over 3 kcal mol\(^{-1}\) for sp\(^{2}\)- and sp\(^{3}\)-hybridised boronic ester substituents (Table S12). To gain insight into the products of origin, sp\(^{3}\)-Si and C-B bond breaking transition states (TSs) 9a and 9b were located and their relative energies determined (Table 3). For aliphatic substrates, the R group was modelled as a methyl substituent to reduce the number of possible conformations. In this case, the C-Si bond breaking TS was favoured by over 9 kcal mol\(^{-1}\) relative to the C-B bond breaking TS (entry 1), indicating a strong preference for the vinyl boronic ester product, as observed. For substrate 1n, with a p-methoxyphenyl substituent, the C-Si bond breaking TS was favoured by 1.2 kcal mol\(^{-1}\) (entry 2), whilst for indolyl substrate 1o the TSs were separated by only 0.2 kcal mol\(^{-1}\) (entry 3). On the other hand, for p-trifluoromethylphenyl substrate 1q, the C-B bond breaking TS was favoured by 1.4 kcal mol\(^{-1}\) (entry 4), and in the case of styrenyl boronic ester 1s, this increased to 5.6 kcal mol\(^{-1}\) (entry 5). These calculated TS energies are in good agreement with the experimentally observed product distributions. The results can be understood by considering how the developing negative charge on carbon is stabilized in the TS of the vinyl boronic esters. Indeed, our calculations show negative charge on carbon is stabilized in the TS of the vinyl boronic esters.
that boron is better able to stabilize negative charge than silicon by 9.1 kcal mol\(^{-1}\) (Table S10). However, for substrates that already bear anion stabilizing groups, elimination takes place preferentially at the more Lewis acidic boron atom, leading to the vinyl silane products.

**Table 3.** Comparison of C-Si and C-B bond breaking TSs for vinyldienation of MeBpin (1t), 1n, 1o, 1q and 1r. B3LYP-D3(BJ)/6-311G(d,p)=IEFPCM(n-pentane)\(/\)B3LYP/6-31G(d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>(\Delta G^\ddagger) (kcal/mol)</th>
<th>C-Si / C-B</th>
<th>Experimental C-Si / C-B</th>
<th>TS(C-B) R = Me</th>
<th>TS(C-B) R = Me</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>0 / 9.2</td>
<td>100:0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(\pm)MeOC(_4)H(_4)</td>
<td>0 / 1.2</td>
<td>100:0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>indanyl</td>
<td>0.2 / 0</td>
<td>53:47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(\pm)CF(_3)C(_2)F(_4)</td>
<td>1.4 / 0</td>
<td>0:100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>styryl</td>
<td>5.6 / 0</td>
<td>100:0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Aliphatic boronic esters gave exclusively the vinyl boronic ester products. The C-Si and C-B bond breaking TSs for 9t \((R = \text{Me})\) are shown.

Finally, we sought to apply our chemistry in natural product synthesis. We were attracted to machillone (10a), a bis-sterol epoxide isolated from the stem wood of *machilus zuhoensis* (Figure 2A), because it showed significant anticancer activity.\[^{[31]}\] Furthermore, the relative configuration of the molecule remained unknown, apart from the epoxide groups, which were assigned as trans from analysis of the coupling constants \((J = 2.4 \text{ Hz})\). From the reported data, it was apparent that the molecule was neither C\(_2\)-symmetric (\(^{1}H\) and \(^{13}C\) NMR data) nor meso (\(\Delta\alpha\) = +22.2°), allowing us to eliminate six of the possible eight diastereoisomers. Based on chemical shift differences between the methylene protons, Breit assigned the methyl substituents of 10a as having an anti-relationship (\(\Delta\delta = 0 \text{ ppm observed}, \Delta\delta > 0.5 \text{ ppm for the syn isomer}\)).\[^{[32]}\] Compound 10b was recovered in 34\% yield together with migratory insertion product 19 in 69\% yield. We therefore investigated alternative conditions and found that using Pd(H\(_{2}\))Cl\(_2\) and K\(_2\)PO\(_4\) in dioxane/water gave tetraene 11 in 69\% yield with significant decomposition,\[^{[24]}\] thus the reported data, it was apparent that the molecule was neither trans nor meso (\(\Delta\alpha\) = +22.2°), allowing us to eliminate six of the possible eight diastereoisomers.

The end game was particularly challenging and required (i) the selective reaction of the styrene over the 1,1-disubstituted alkene (ii) reagent-controlled diastereoselective epoxidation (iii) isolation of the monoepoxide from the statistical mixture of SM, mono- and di-epoxides that would be expected. Following this reaction, a second epoxidation of the monoepoxide with the enantiomerically pure epoxidation reagent should occur on the remaining styrene with the correct stereochemical outcome. Our initial attempts were based around the Shi epoxidation but no conversion to the desired mono-epoxide 19 was observed and instead starting material was recovered.\[^{[26]}\] We then explored the Sharpless dihydroxylation,\[^{[57]}\] a reaction where styrenes are known to be more reactive than 1,1-disubstituted alkenes.\[^{[38]}\] To our delight, the reaction provided diol 20 in 34\% yield, with excellent diastereoselectivity, and with no evidence of reaction at the 1,1-disubstituted double bond. Starting material 11 was recovered in 37\% yield and the C\(_2\)-symmetric bis-dihydroxylation product 21 was obtained in 18\% yield. After a second dihydroxylation reaction using the pseudo-enantiomeric reagent and subsequent ring-closing,\[^{[39]}\] the target molecule was obtained.

Unfortunately, upon comparison of the reported NMR data with that of our synthetic sample, significant differences were observed. The considerable deviations (see S.I. for tabulated data) led us to the conclusion that the issue was not related to stereochemistry, but instead was likely due to a misassignment in the connectivity of the molecule. Further efforts to elucidate the structure of machillone are currently underway in our laboratory using a combination of computational and synthetic methods.

In summary, we have developed a new protocol for the vinyldienation homologation of boronic esters that provides access to a diverse range of 1,1-disubstituted and trisubstituted vinyl boronic esters. Computational studies have revealed that both the Peterson and Wittig pathways are feasible, but the Peterson pathway is more likely (Figure S7). Our retrosynthetic analysis began with sequential epoxidation reactions from tetraene 11. We envisaged the carbon skeleton would be constructed through a bidirectional approach from methylene diboron (14), comprised of homologations with lithiated TIB ester 13**[^{[33]}\]** and lithiated epoxysilane 4a, followed by a Pd-catalysed allylic cross-coupling reaction. If successful, the route would give access to machillone in just 6 steps from commercially available diboron 14, and without the need for protecting groups.

Our synthesis began with homologation of 14 with lithiated species 13, giving bis-boronic ester 15 in 83\% yield, and as a single diastereoisomer (Figure 2B). The vinyldienation reaction gave bis-vinyl boronic ester 16 in 58\% yield together with mono-vinyl boronic ester 17 in 9\% yield. The next step involved a Pd-catalysed allylic cross-coupling reaction between 16 and allylic acetate 12. To our knowledge there is just a single report that describes the coupling of a vinyl boronic ester with an allylic acetate, however these conditions (PdCl\(_2\)/TFP, KF, MeOH, rt) led to a low yield of 11 with significant decomposition,\[^{[24]}\] thus the reported NMR data, it was apparent that the molecule was neither trans nor meso (\(\Delta\alpha\) = +22.2°), allowing us to eliminate six of the possible eight diastereoisomers.

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In summary, we have developed a new protocol for the vinyldienation homologation of boronic esters that provides access to a diverse range of 1,1-disubstituted and trisubstituted vinyl boronic esters. Computational studies have revealed that both the Peterson and boron-Wittig pathways are feasible but the Peterson pathway is favoured because boron can better stabilize the negative charge developing on the α-carbon in the transition-state of the elimination step. The methodology was used in a short, stereoselective synthesis of machillone but, upon comparing the reported and synthetic NMR data, it was clear that the structure of the natural product had been mis-assigned.

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**Keywords:** organoboron • homologation • stereospecific • natural product • vinyl boronic ester
Figure 2. A) Structure determination and retrosynthesis of machillene. B) Total synthesis of the proposed structure of machillene.


Vinylidene boronic esters can be obtained by the homologation of boronic esters with lithiated epoxysilane in a process where the selectivity for the vinyl boronic ester or vinyl silane product depends on the anion stabilizing ability of the R group. The methodology was applied in a short stereoselective synthesis of the proposed structure of machillene, however, synthetic and reported data did not match.