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ABSTRACT: Simple propargylic silyl ethers can be converted to complex cyclopropyl boronic acid pinacol esters in an efficient one-pot procedure. Terminal acetylenes undergo a Schwartz’s Reagent catalysed hydroboration; subsequent addition of further Schwartz’s Reagent and Lewis acid mediated activation of neighbouring silyl ether, allows cyclisation to access a range of cyclopropyl boronic acid pinacol esters. The scope includes aromatic, aliphatic, quaternary and spiro substituted cyclopropyl rings which can be transformed via Suzuki coupling into a range of lead-like substituted cyclopropyl aryl products.

Cyclopropyl rings are ubiquitous motifs in natural products and bioactive molecules1a-e (Scheme 1), with their three-dimensional character offering novel vectors for substitution.

Scheme 1. Structures of selected marketed drugs

A number of methods for synthesis have been developed, including Simmons-Smith cyclopropanation,2a-b Pd-catalysed diazomethane addition3 and Corey-Chaykovsky cyclopropanation.4a-c Due to the high synthetic utility of pinacol boronic esters,5 our focus was the synthesis of cyclopropyl rings containing this functionality to facilitate straightforward incorporation into bioactive scaffolds. Established methodologies and reported approaches to these key building blocks include cyclopropanation of vinyl pinacol boronic esters,6 hydroboration of cyclopropene rings7 or C-H activation borylation of a preformed cyclopropyl ring.8

Methodology whereby cyclopropyl ring and boron species are introduced in the same sequence are also possible. These include cyclopropanation using a modified Simmons-Smith reagent9 and asymmetric copper(I) catalysed borylation cyclisation10 (Scheme 2). However all of these methods are limited by scope, modularity and/or starting material tractability.


Of initial interest, was the cyclopropanation methodology developed by Szymoniak (Scheme 3).11 Here, a hydrozirconation followed by Lewis acid mediated cyclisation yields a range of substituted cyclopropyl rings. Use of Schwartz’s Reagent is an established method for alkene and alkynie activation via a hydrozirconation to form an organozirconium species.12 The resulting complex can then be transformed using various reaction manifolds such as addition to an electrophile13a-c or transmetallation.14a-c

This led us to the hypothesis that the methodology developed by Szymoniak could be applied to vinyl pinacol boronic esters, since the synthesis of gem-borazirconocene complexes has been reported.15a-b We further reasoned that
these vinyl pinacol boronic esters could be generated in situ from the corresponding alkyne (Scheme 3).

**Scheme 3. Methodology for cyclopropyl ring synthesis developed by Szymoniak and the reaction developed in this work. Proposed hydrozirconation approach.**

Based on all of the above, initial studies focused on the model substrates 3a-d and synthesis of the simplest cyclopropyl pinacol boronic ester 4.

**Table 1. Optimisation of conditions for one-pot borylation cyclisation methodology.**

<table>
<thead>
<tr>
<th>Substrate R =</th>
<th>Eq.</th>
<th>Cp₂ZnCl₂</th>
<th>BF₃.OEt₂</th>
<th>Yield%</th>
<th>Yield% 5a-d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>1</td>
<td>2</td>
<td>43</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bu</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>TBDMS</td>
<td>3</td>
<td>2</td>
<td>66</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TBDMS</td>
<td>6</td>
<td>0.5</td>
<td>77</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*With reference to bistrimethylsilylbenzene internal standard. *No conversion to intermediate vinyl BP 5 was observed.

Deuterated solvents were used to allow facile analysis of reaction milieu by NMR.

Initial studies using methyl propargyl ether 3a led to encouraging results with modest conversion to product 2 observed by NMR with additional vinyl pinacol boronic ester intermediate 5a remaining. After a limited solvent screen (see Supporting Information), dichloromethane was found to be optimal and hence was selected for further studies. Exploration of the stoichiometry of Schwartz’s Reagent in an attempt to promote hydrozirconation onto the hindered vinyl pinacol boronic ester intermediates 5a-d led to three equivalents being selected as it resulted in high conversion to cyclopropyl product 2, with only low amount of intermediate 5a-d remaining. Next, a range of potential leaving groups were examined with the silyl ether systems proving to be optimal (Table 1). We hypothesise that the availability of low-lying empty orbitals at the silicon centre result in a better leaving group and a more facile cyclisation.

Pleasingly, upon application of conditions to more complex 4-bromo-phenyl system a similar levels of conversion were observed, however as a mixture of diastereoisomers, which could not easily be separated by chromatography. Further studies were then carried out to explore the effect of silyl ether group on diastereomeric ratio. It was reasoned that variation of size of group would affect the approach of Schwartz’s Reagent to the vinyl pinacol boronic ester intermediate. Variation in diastereomeric ratio was observed dependent on the size of silyl protecting group (Table 2) with largest tris(dimethylphenyl)silyl group yielding predominantly cis-diastereoisomer (3:8:1) and smallest triethoxysilyl yielding major trans-diastereoisomer (0:4:1). However, selectivity could not be improved further and reduced yields were observed. This led to the tert-butyl(dimethylsilyl) group being selected for further study.

**Table 2. Influence of size of silyl group on diastereomeric ratio.**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R =</th>
<th>Yield %</th>
<th>cis:trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>Me</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>29</td>
<td>SMe</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>29</td>
<td>Bu</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>29</td>
<td>TBDMS</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>30</td>
<td>TBDMS</td>
<td>43</td>
<td>21</td>
</tr>
</tbody>
</table>

With optimised conditions for the conversion in hand, we next investigated the scope of the one-pot borylation cyclisation reaction. A variety of silyl ethers were selected containing a range of electron rich and electron poor benzylic ethers, aliphatic ethers and quaternary ethers.

A number of benzylic substituted propargyl ethers could be converted with both electron donating and electron withdrawing substituents (9a-e). It was observed that the electronic properties of the aryl substituents influence diastereomeric ratio (9b, 4:3:1 to 9a, 0.4:1). The reaction was found to be dependent on steric with a reduction in yield observed from phenyl 9e (66%) to ortho-tolyl 9f (29%) to 2,6-dimethylphenyl 9g (10%). From consideration of the reaction profile it can be inferred that steric bulk appears to inhibit initial zirconium catalysed hydroboration step. The reaction was also found to proceed for aliphatic substituents ethyl phenyl 9h (59%) and ethyl furanyl 9i (58%). With more challenging quaternary substituted centers, product formation was observed in slightly reduced yield, 2-methyl-2-phenyl 9j (34%). No formation of product was observed for pyridine containing functionality 9k, despite observation of vinylidene boronic ester intermediate—a the reaction mixture being confirmed possibly due to coordination of nitrogen lone pair to reactive species. The small fused spirocyclic derivative
was also unsuccessful, with high ring strain in the system hypothesised to prevent cyclisation (Scheme 4).\textsuperscript{16a}

Scheme 4. Exploration of scope of one-pot borylation cyclisation reaction.

Having established the generality of the process, we next sought to demonstrate the one pot generation of a diverse range of products relevant to medicinal and agrochemical efforts. These syntheses were telescoped utilising a Suzuki-Miyaura cross coupling protocol following on from the initial cyclopropanation (Scheme 5).\textsuperscript{19} Simple propargylic ether starting materials could easily be converted in one-pot to bis-substituted cyclopropyl rings with electron donating,\textsuperscript{11a} or electron withdrawing,\textsuperscript{11b} substituents. Lead-like spiro-cyclopropyl fragments could also be prepared, yielding products 11c and 11d in around 25% yield over four reaction steps (71% average yield per step). Spiro compounds derivatives\textsuperscript{11c} and 11d are of interest in bioactive compounds as they exhibit a significant degree of 3D character\textsuperscript{20} and conformationally constrained growth vectors for drug discovery.\textsuperscript{21} The method was also used to synthesise the bis-cyclopropyl derivative 11e, an intermediate in the synthesis of bioactive compound Sedaxane.\textsuperscript{13}

Sedaxane is a succinate dehydrogenase inhibitor and is effective in producing higher and more consistent yields of major crops, such as cereals and soybean.\textsuperscript{22a-b} Deprotection and amide coupling of bocBoc-aniline 12 yields Sedaxane 13 in overall 8 linear steps 4% yield, whilst high temperature cyclisation involved in Kischner route\textsuperscript{23a-b} developed by Syngenta.\textsuperscript{24} This route allows a modular construction of the bicyclopropyl template making late stage diversification of the system possible.


Next, in the final part of our study, we sought to explore the mechanism of the exemplified reaction. Use Application of chiral substrates enabled us to explore the mechanism of the Lewis acid mediated cyclisation. Our research shows this work indicates that racemisation does not occur during the reaction, as both target compounds 15a and 15b are isolated in high enantiopurity. This enables synthesis of chiral cyclopropyl boronic esters starting from readily accessible chiral propargylic alcohols. These can easily be

*Diastereomers could be separated by reverse phase chromatography.

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Experimental procedures and characterisation of all compounds suggest that the process is invertive at the alcohol centre for substrate 14a. We therefore propose a mechanism in contrast to that proposed by Szymoniak (Scheme 6).  

Scheme 6. Application of methodology to chiral substrates and proposed mechanism for key step.

In conclusion, our methodology allows the conversion of synthetically tractable propargylic alcohols to a range of aryl, aliphatic, quaternary and spiro substituted cyclopropyl pinacol boronic esters using commercial reagents. This transformation allows access to a range of complex building blocks for synthesis, allowing modular construction of cyclopropyl scaffolds. Further work is ongoing to explore optimisation of diastereomeric ratio.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterisation of all compounds (PDF)

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Notes
The authors declare no competing financial interests.

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REFERENCES


(17) (a) Benoît, G.; OTH And OTHz were found to be unstable to zirconium-hexanedihydroborate. (b) Conversion to vinyl boronic ester intermediate was observed by $^1$H NMR on an aliquot taken after completion of step i) (c) Reaction was also unsuccessful upon addition of 2 eq. BF$_3$OEt$_2$.  


