One-Pot, Three Step Synthesis of Cyclopropyl Boronic Acid Pinacol Esters from Synthetically Tractable Propargylic Silyl Ethers.

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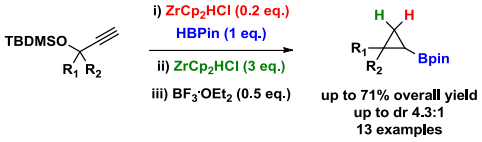
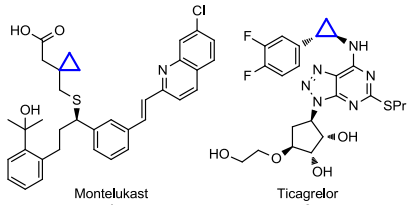
~~*Supporting Information Placeholder*~~

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 molecules[1a-e] (**Scheme 1**), with their three-dimensional character offering novel vectors for substitution.

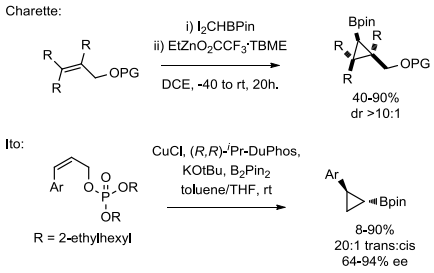
Scheme 1. Structures of selected marketed drugs



A number of methods for synthesis have been developed, including Simmons-Smith cyclopropanation,[2a-b] Pd-catalysed diazomethane addition[3] and Corey-Chaycovsky 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 methodology~~Reported approaches to these key building blocks include cyclopropanation of vinyl pinacol boronic esters,[6] hydroboration of cyclopropene rings[7] 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 reagent[9] and asymmetric copper(I) catalysed borylation cyclisation[10] (**Scheme 2**). However all of these methods are limited by scope, modularity and/or starting material tractability.

Scheme 2. A selection of methods for preparing cyclopropyl pincaol boronic ester derivatives.

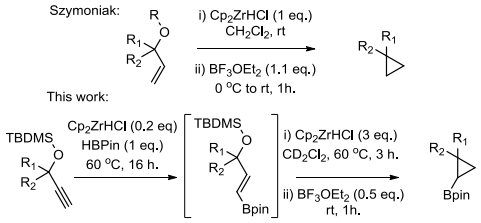


Of initial interest, was the cyclopropanation methodology developed by Szymoniak (**Scheme 3**).[11] Here, a hydrozirconation followed by Lewis acid mediated cyclisation yields a range of substituted cyclopropyl rings. Use of Schwartz's Reagent is an established method for alkene and alkyne activation *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 electrophile[13a-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

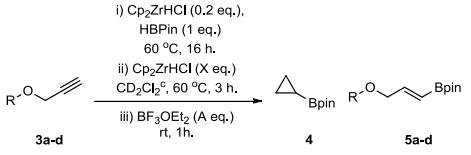
these vinyl pinacol boronic esters could be generated *in situ* from the corresponding alkyne (**Scheme 3**).[16a-b]

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.



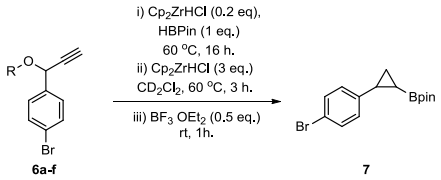
	Substrate R =	Eq. Cp_2ZrHCl	Eq. BF_3OEt_2	Yield[a] **4**	Yield[a] **5a-d**
1	Me	1	2	43	21
2	Me	3	2	50	4
3	H	3	2	-[b]	-
4	Bn	3	2	61	0
5	TBDMS	3	2	66	1
6	**TBDMS**	**3**	**0.5**	**77**	**0**

[a]With reference to bistrimethylsilylbenzene internal standard. [b]No conversion to intermediate vinyl BPin **5** was observed. [c]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~~**4**, 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**).[17] 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 ~~was~~ 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 tristrimethyl 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 (see **Supporting Information**). This led to the *tert*-butyldiemthylsilyl group being selected for further study.

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



	R =	Cis:Trans
1	$Si(OEt)_3$	0.4 : 1
2	$SiEt_3$	0.6 : 1
3	Si^tBuPh_2	1.1 : 1
4	Si^tBuMe_2	1.2 : 1
5	Si^iPr_3	1.5 : 1
6	$Si(SiMe_3)_3$	3.8 : 1

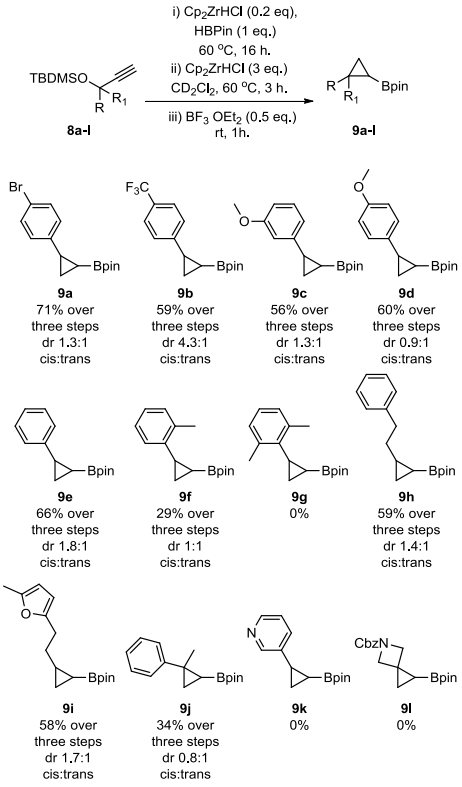
Commented [CJ1]: add compound #'s to table e.g. 3a, 3b etc

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 propargylic ethers could be converted with both electron donating and electron withdrawing substituents **(9a-e)**. It was observed that the electronic properties of the aryl subtituents influence diastereomeric ratio (**9b**, 4.3:1 to **9d,** 0.9:1). The reaction was found to be dependent on sterics with a reduction in yield observed from phenyl **9e** (66%) to *ortho*-tolyl **9f** (29%) to 2,6-dimethylphenyl **9g** (0%). 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 vinylic boronic ester intermediate—in the reaction mixture~~being confirmed~~,[18a] possibly due to coordination of nitrogen lone pair to reactive species.[18b] The ~~S~~small fused spirocyclic derivative

9l was also unsuccessful, with high ring strain in the system hypothesised to prevent cyclisation (**Scheme 4**).[18a]

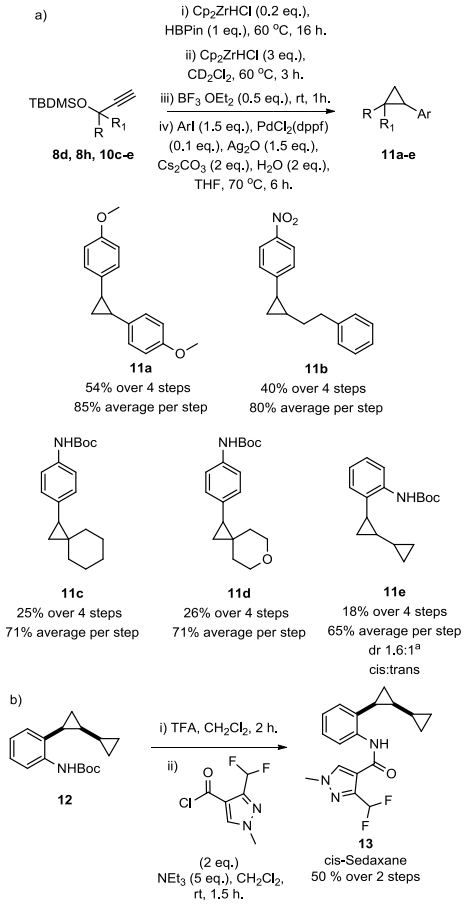
Scheme 4. Exploration of scope of one-pot borylation cyclisation reaction.



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**).[19] Simple propargylic ether starting materials could easily be converted in one-pot to bis-substituted cyclopropyl rings with electron donating, **11a** or election withdrawing, **11b**, substiuents. 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 **11c** and **11d** are of interest in bioactive compounds as they exhibit a significant degree of 3D character[20] and conformationally constrained growth vectors for drug discovery.[21] The method was also used to synthesise the bis-cyclopropyl derivative **11e**, an intermediate in the synthesis of bioactive compound Sedaxane **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.[22a-b] Deprotection and amide coupling of ~~boc~~Boc-aniline **12** yields Sedaxane **13** in overall 8 linear steps 4% yield, whilst high temperature cyclisation involved in Kischner route[23a-b] developed by Syngenta.[24] This route allows a modular construction of the bicyclopropyl template making late stage diversification of the system possible.

Scheme 5a). Diversification of cyclopropyl boronic ester products in a Suzuki-Miyaura cross coupling. b) Synthesis of cyclopropyl containing fungicide, Sedaxane.



[a]Diastereomers could be separated by reverse phase chromatography.

~~Next,~~In the final part of our study, we sought to explore the mechanism of the exemplified reaction. ~~Use~~ Application of chiral substrates ~~allowed~~ enabled us to ~~explore~~ probe the mechanism ~~for~~ of the Lewis acid mediated cyclisation. ~~Our research shows~~This work inidcates 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

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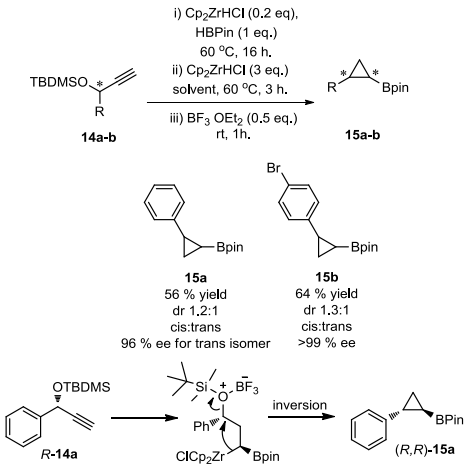
prepared ~~according to numerous~~through asymmetric ~~chiral~~ additions of alkynes to aldehyde or ketone[25a-c] derivatives, or *via* chiral reduction of propargylic ketones.[26] Our results suggest that the process is invertive at the alcohol centre for substrate **14a**. We therefore propose a mechanism in contrast to that proposed by Szymoniak (**Scheme 6**).[11]

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 containing fragments. These can then be reacted to yield drug-like 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.

ACKNOWLEDGMENT

Financial support for this work was provided by GSK *via* the GSK/University of Strathclyde Centre for Doctoral Training in Synthetic and Medicinal Chemistry.

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(17) OH, OTs, OTHP And OBz were found to be unstable to zirconium mediated hydroboration.

(18) (a) Conversion to vinyl boronic ester intermediate was observed by ^{1}H NMR on an aliquot taken after completion of step i) (b) Reaction was also unsuccessful upon addition of 2 eq. BF_3OEt_2.

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