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

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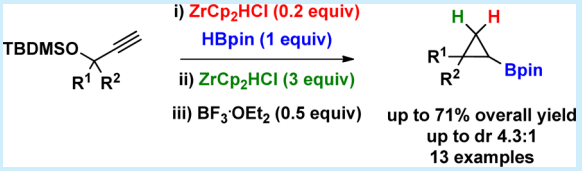
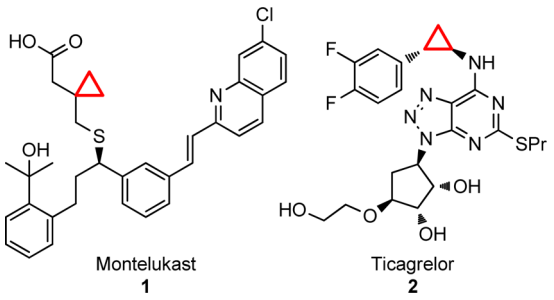
Supporting Information

ABSTRACT: Simple propargylic silyl ethers can be converted to complex cyclopropylboronic acid pinacol esters in an efficient one-pot procedure. Terminal acetylenes undergo a Schwartz's reagent catalyzed hydroboration; subsequent addition of further Schwartz's reagent and Lewis acid-mediated activation of neighboring silyl ether allows cyclization to access a range of cyclopropylboronic 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.

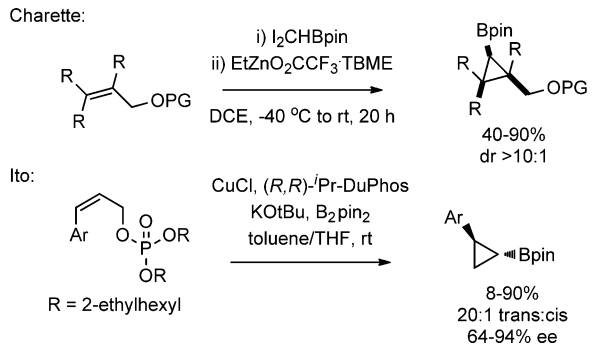
Scheme 1. Structures of Selected Marketed Drugs



A number of methods for synthesis have been developed including Simmons-Smith cyclopropanation,[2a,b] Pd-catalyzed diazomethane addition,[3] and Corey-Chaykovsky cyclopropanation.[4a−c] Because of the high synthetic utility of pinacol boronic esters,[5] our focus was the synthesis of cyclopropyl rings containing this functional unit to facilitate straightforward incorporation into bioactive scaffolds. 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]

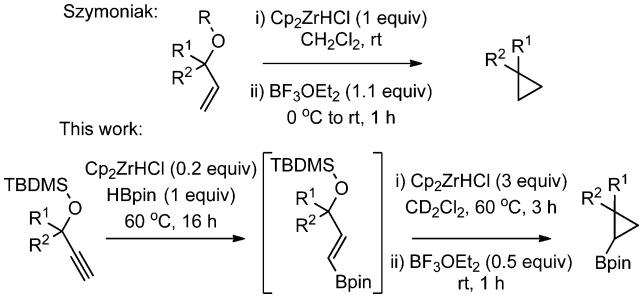
Methods whereby the cyclopropyl ring and boron species are introduced in the same sequence are also possible. These include cyclopropanation using a modified Simmons-Smith reagent[9] and asymmetric copper(I)-catalyzed borylation/cyclization[10] (Scheme 2). However, all of these methods are limited by scope, modularity, or starting material tractability.

Scheme 2. Selection of Methods for Preparing Cyclopropylpinacol Boronic Ester Derivatives[a]



[a]TBME = 2-methoxy-2-methylpropane.

Scheme 3. Proposed Hydrozirconation Approach



Of initial interest was the cyclopropanation method developed by Szymoniak (Scheme 3).[11] Here, a hydrozirconation followed by Lewis acid-mediated cyclization yields

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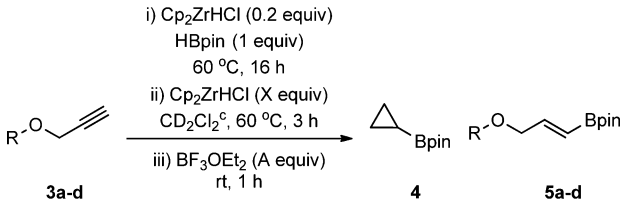
a range of substituted cyclopropyl rings. The use of Schwartz's reagent is an established method for alkene and alkyne activation via a hydrozirconation to form an organozirconium species.[12] The resulting complex can then be transformed using various reaction manifolds such as addition to an electrophile[13a−c] or transmetalation.[14a−c]

This led us to the hypothesis that the method 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]

On the basis of all of the above, initial studies focused on the model substrates **3a−d** and synthesis of the simplest cyclopropyl pinacol boronic ester **4**.

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 **4**, with only a low amount of intermediate **5a−d** remaining. Next, a range of potential leaving groups was examined with the silyl ether systems proving to be optimal (Table 1).[17] We hypothesize that the availability of low-lying empty orbitals at the silicon center resulted in a better leaving group and a more facile cyclization.

Table 1. Optimization of Conditions for One-Pot Borylation Cyclization Method



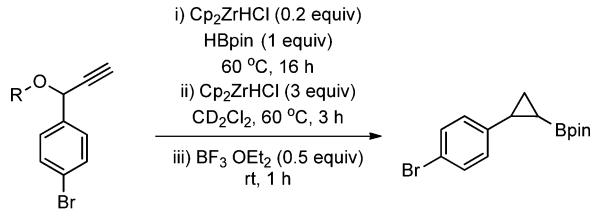
3a-d **4** **5a-d**

	substrate (R =)	equiv Cp_2ZrHCl	equiv BF_3OEt_2	yield[a] (%) **4**	yield[a] (%) **5a−d**
1	**3a** (Me)	1	2	43	21
2	**3a** (Me)	3	2	50	4
3	**3b** (H)	3	2	-[b]	-[b]
4	**3c** (Bn)	3	2	61	0
5	**3d** (TBDMS)	3	2	66	1
6	**3d** (TBDMS)	3	0.5	77	0

[a]With reference to bis(trimethylsilyl)benzene internal standard. [b]No conversion to intermediate vinyl Bpin **5b** was observed. [c]Deuterated solvents were used to allow facile analysis of reaction milieu by NMR.

Pleasingly, upon application of conditions to more complex 4-bromophenyl system, 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 this 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 the silyl protecting group (Table 2).

Table 2. Influence of Size of Silyl Group on Diastereomeric Ratio



6a-f **7**

	substrate (R =)	*cis*/*trans*
1	**6a** ($Si(OEt)_3$)	0.4:1
2	**6b** ($SiEt_3$)	0.6:1
3	**6c** (Si^tBuPh_2)	1.1:1
4	**6d** (Si^tBuMe_2)	1.2:1
5	**6e** (Si^iPr_3)	1.5:1
6	**6f** ($Si(SiMe_3)_3$)	3.8:1

The largest tristrimethylsilyl group yielded predominantly *cis*-diastereoisomer (3.8:1), and the smallest triethoxysilyl yielded predominantly *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*-butyldimethylsilyl group being selected for further study.

With optimized conditions for the conversion in hand, we next investigated the scope of the one-pot borylation/cyclization 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 (**7**, **9a−d**). It was observed that the electronic properties of the aryl substituents influence the diastereomeric ratio (**9a**, 4.3:1 to **9c**, 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 **9e** (29%) to 2,6-dimethylphenyl **9f** (0%). From consideration of the reaction profile, it can be inferred that steric bulk appears to inhibit initial zirconium catalyzed hydroboration step. The reaction was also found to proceed for aliphatic substituents ethyl phenyl **9g** (77%) and ethyl furanyl **9h** (58%). With more challenging quaternary substituted centers, product formation was observed in slightly reduced yield, 2-methyl-2-phenyl **9i** (34%). No formation of product was observed for pyridine containing product **9j**, despite observation of a vinylic boronic ester intermediate in the reaction mixture,[18a] possibly due to coordination of nitrogen lone pair to reactive species.[18b] The small fused spirocyclic derivative **9k** was also unsuccessful, with high ring strain in the system hypothesized to prevent cyclization (Scheme 4).[18a]

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 utilizing 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

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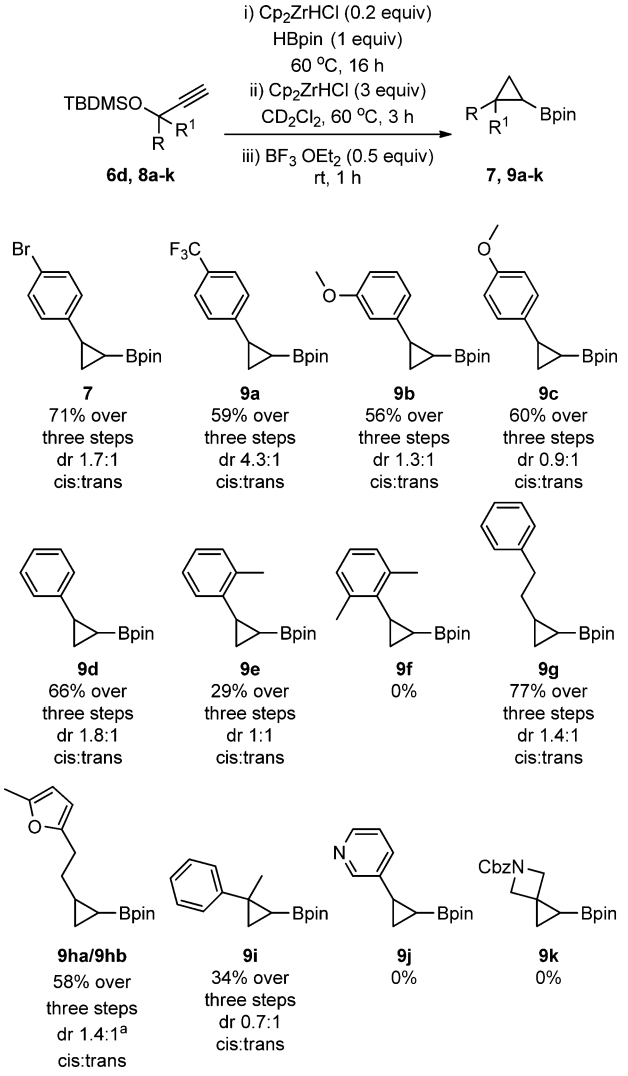
Scheme 4. Exploration of Scope of One-Pot Borylation/Cyclization Reaction

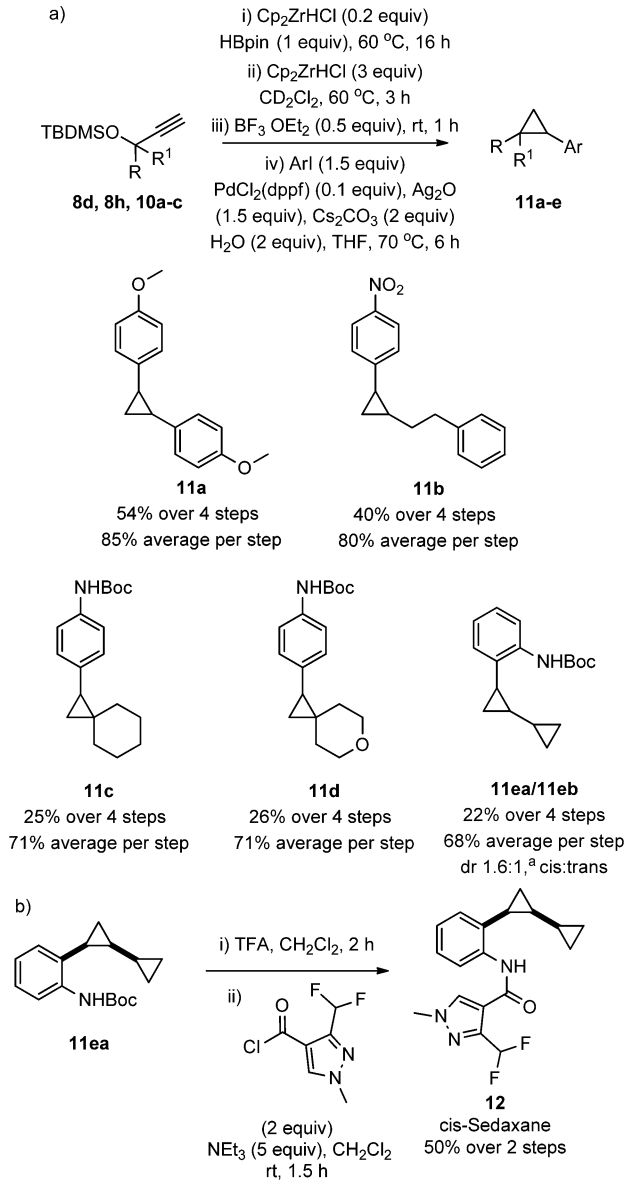


election-withdrawing, **11b**, substituents. Lead-like spiro-cyclopropyl fragments could also be prepared, yielding products **11c** and **11d** in around 25% yield over four reaction steps (71% average yield per step). Spiro derivatives **11c** and **11d** are of interest in bioactive compounds as they exhibit a significant degree of 3D character[20] and conformationally constrained growth vectors for drug discovery.[21] The method was also used to synthesize the bis-cyclopropyl derivative **11e**, an intermediate in the synthesis of bioactive compound Sedaxane **12**.

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-aniline **11ea** yields Sedaxane **12**. This route allows a modular construction of the bicyclopropyl template making late stage diversification of the system possible.

In the final part of our study, we sought to explore the mechanism of the exemplified reaction. Application of chiral substrates enabled us to probe the mechanism of the Lewis acid-mediated cyclization. This work indicates that racemization does not occur during the reaction as both target compounds **14a** and **14b** are isolated in high enantiopurity.

Scheme 5. (a) Diversification of Cyclopropylboronic Ester Products in Suzuki-Miyaura Cross-Coupling; (b) Synthesis of Cyclopropyl-Containing Fungicide, Sedaxane



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

This enables synthesis of chiral cyclopropylboronic esters starting from readily accessible chiral propargylic alcohols. These can easily be prepared through asymmetric addition of alkyne systems to aldehyde or ketone[23a−c] derivatives or via chiral reduction of propargylic ketones.[24] Our results suggest that the process is invertive at the alcohol center for substrate **13a**. We therefore propose a distinct mechanism in contrast to the stereoretentive mechanism proposed by Szymoniak (Scheme 6).[11]

In conclusion, our method 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 and allows modular construction of cyclopropyl-containing fragments. These can then be reacted to yield

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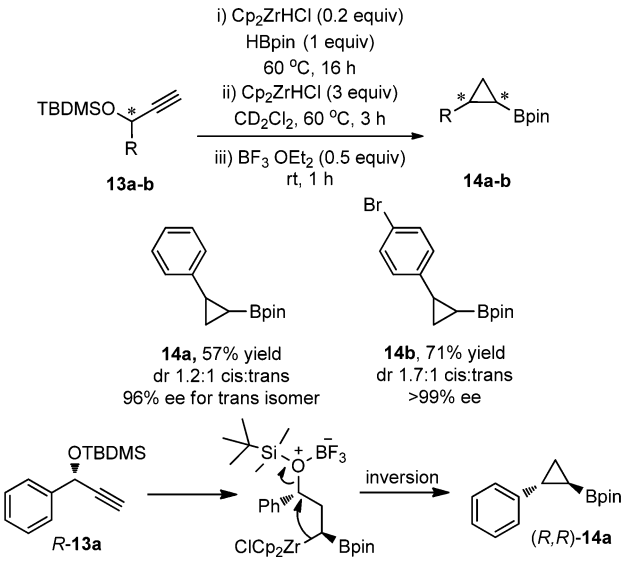
Scheme 6. Application of Methodology to Chiral Substrates and Proposed Mechanism for Key Step



drug-like scaffolds. Further work is ongoing to explore optimization of the diastereomeric ratio.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01778.

Experimental procedures; characterization of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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

(18) (a) Conversion to a 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 equiv BF_3·OEt_2.

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