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Diastereoselective Borocyclopropanation of Allylic Ethers Using a Boromethylzinc Carbenoid

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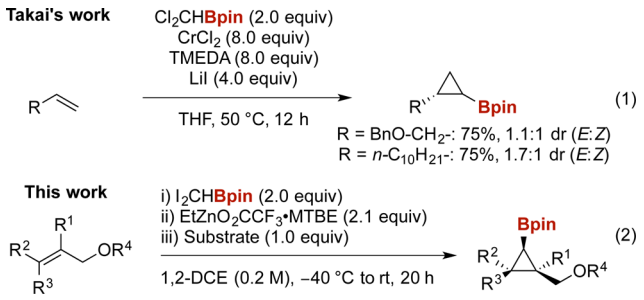
Supporting Information

ABSTRACT: A borocyclopropanation of (*E*)- and (*Z*)-allylic ethers and styrene derivatives via the Simmons–Smith reaction using a novel boromethylzinc carbenoid is described. The carbenoid precursor is prepared via a 3-step sequence from inexpensive and commercially available starting materials. This methodology allows for the preparation of 1,2,3-substituted borocyclopropanes in high yields and diastereoselectivities. Several postfunctionalization reactions were also performed to illustrate the versatility of these building blocks.

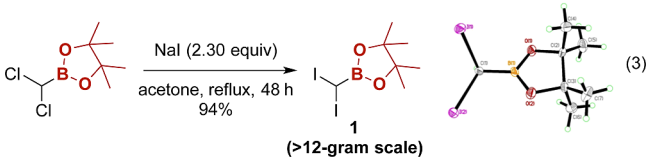
Mono- and disubstituted cyclopropane rings have been incorporated in pharmaceutically relevant compounds and are now routinely included in SAR studies of new drug candidates in order to modulate their activity, metabolism or conformational rigidity.[1,2] Moreover, some of these subunits are often embedded in peptide backbones. Indeed, β-turn/hairpins or others were found to behave as isosteres of amino acid side-chains.[3] Conversely, 1,2,3-trisubstituted cyclopropane units are present in many biologically active natural products.[4] Direct access to these highly substituted cyclopropanes from alkenes is not always straightforward through conventional routes: (1) their syntheses require diazo or dihalide carbenoid precurors that are not easily prepared and highly reactive, and (2) their reactivity is very dependent on their degree of substitution.[5] Novel powerful strategies to access highly substituted cyclopropane derivatives are highly desirable.

An attractive and divergent strategy toward 1,2,3-trisubstituted cyclopropanes consists of installing a reactive synthetic handle on a cyclopropyl moiety that allows for rapid diversification of a common intermediate toward multiple classes of cyclopropanes. Borocyclopropanes can serve this role; they represent key synthetic building blocks for the integration of the cyclopropyl motif onto complex frameworks through the Suzuki–Miyaura cross-coupling reaction. Several strategies have been developed to access cyclopropylboronic acids. The most common approaches are lithium/halogen exchange followed by trialkylborate trapping,[6] cyclopropanation of vinylboronates,[7,8] enantioselective Rh-catalyzed hydroboration of cyclopropenes,[9] C–H borylation of cyclopropanes,[10] and borometalation/cyclization of *Z*-allylic phosphonates.[11] Takai has also shown that treatment of an alkene with dichloropinacolboronate and excess chromium(II) chloride results in the formation of borocyclopropane, albeit with low diastereoselectivities (eq 1).[12] In this Communication, we report an efficient synthesis of



borocyclopropanes in a single step through the direct borocyclopropanation of olefins via the use of a novel boronate-substituted zinc carbenoid (eq 2).[13]

Because dichloromethylpinnacol boronate could not be used as the zinc carbenoid precursor, due to the low C–Cl bond reactivity an efficient method for the preparation of the more reactive diiodo precursor was required. We were pleased to find that this compound could be readily prepared from the corresponding dichloromethylpinnacol boronate by a double Finkelstein reaction with NaI in acetone (eq 3).[14] Using this simple procedure, **1** could be prepared on a multigram scale in 60% overall yield in 3 steps starting from dichloromethane and without any flash column chromatography.[15]



We then directed our attention toward optimizing the conditions to generate the boro-substituted carbenoid. Because it was anticipated that this intermediate would be quite unstable because of the lability of C–B bonds in the presence of organozinc reagents,[16] we elected to form the carbenoid in the presence of alkene **2a** (Table 1). Although only traces of borocyclopropane were obtained using Et_2Zn, our first breakthrough came when EtZnI was employed as the zinc source in a Zn:**1** ratio of 1.0:1.0 in DCM. When stirred for 20 h from 0 °C to rt, this reaction provided the desired borocyclopropane **3a** in 43% yield and excellent diastereoselectivities (Table 1, entry 1). After an extensive optimization of the nature of zinc reagent,[17,18] reaction temperature, solvent,

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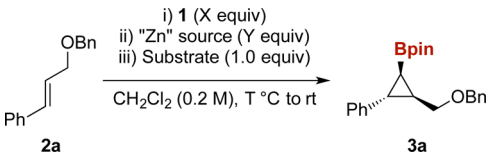
Table 1. Optimization of the Borocyclopropanation Reaction[a]



2a 3a

entry	"Zn"	Y (equiv)	1 (equiv)	T (°C)	yield (%)[b]
1	EtZnI	1.1	1.1	0	43
2	EtZnI·OEt_2	1.1	1.1	0	24
3	EtZnI·MTBE	1.1	1.1	0	51
4	EtZnI·MTBE	1.6	1.5	0	67
5	EtZnOHFIP·MTBE	1.6	1.5	0	67
6	$EtZnOPO_3Bu_2$·MTBE	1.6	1.5	0	0
7	$EtZnOC_6H_2Cl_3$·MTBE	1.6	1.5	0	17
8	$EtZnO_2CCF_3$·MTBE	1.6	1.5	0	42
9	$EtZnOCH_2CF_3$·MTBE	1.6	1.5	0	70
10	$EtZnOCH_2CF_3$·MTBE	2.1	2	0	81
11	$EtZnO_2CCF_3$·MTBE	2.1	2	−40	81
12[c]	$EtZnO_2CCF_3$·MTBE	2.1	2	−40	90[d]

[a]For entry 1, carbenoid generated *in situ* in the presence of **2a**; for entries 2−12, carbenoid generated first followed by addition of **2a**. [b]NMR yields using triphenylmethane as internal standard, for each entry, a 20:1 dr is measured. [c]Reaction performed in 1,2-dichloroethane (0.2 M). [d]Isolated yield.

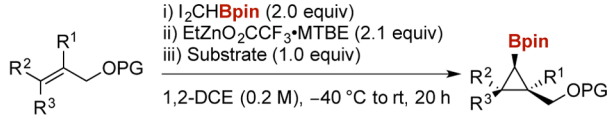
reagents' stoichiometry and additives (Table 1, entries 2−11), the desired borocyclopropane **3a** was obtained in 90% isolated yield after flash chromatography (Table 1, entry 12). Unlike in most of the previously reported cyclopropanation reactions, MTBE was found to be a superior complexing additive than diethyl ether (Table 1, entry 2 vs 3). Further modification of the ethylzinc source indicated that the trifluoroacetate was optimal (entries 4−11).

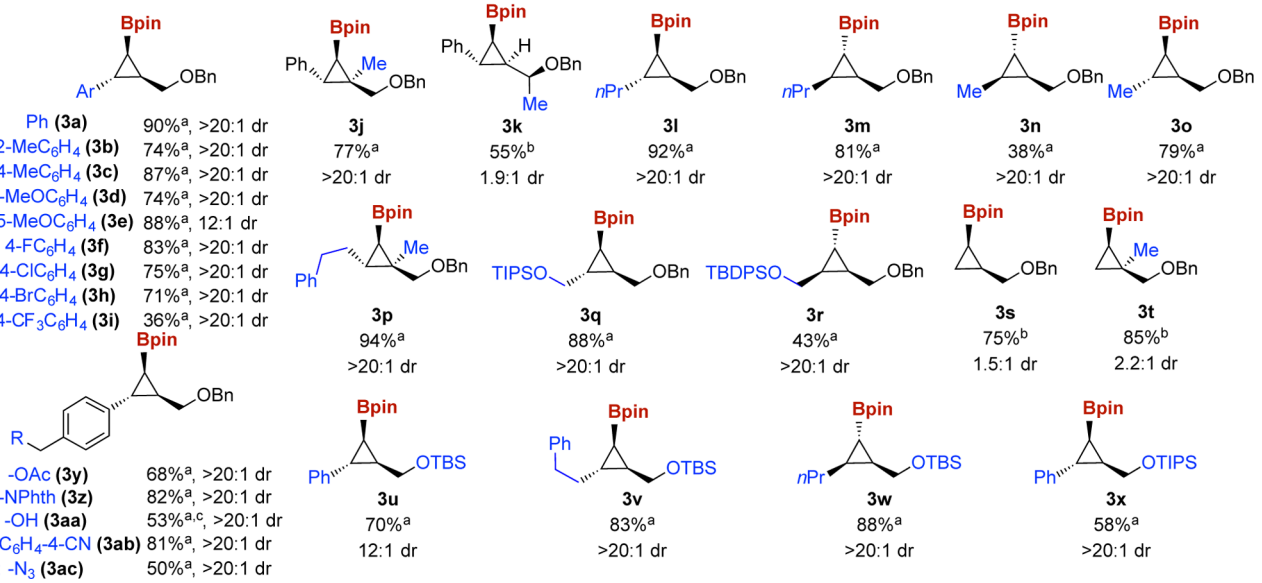
In contrast to the previously reported cyclopropanation reactions using substituted zinc carbenoids, the major product **3a** has the Bpin group *cis* to the benzyl ether side-chain.[19] This structure was confirmed by NOE NMR and X-ray crystallography.

To explore the generality of the optimized conditions, a series of protected allylic alcohols were submitted to our optimized reaction conditions (Scheme 1). Cyclopropanes arising from electron-rich aryl and haloaryl substituents on (*E*)-allylic benzyl ethers were obtained in good yields and excellent diastereoselectivities (**3a**−**3h**). However, the analogous trifluoromethyl substituted product (**3i**) was isolated in lower yield likely due to the decreased nucleophilicity of the starting olefin.

Trisubstituted olefins reacted cleanly to provide **3j** and **3p** in good yields and excellent diastereocontrol. Unfortunately, secondary benzyl ethers (**3k**) were less reactive under the reaction conditions and gave poor selectivities (1.9:1 dr). We also applied the reaction to alkyl-substituted olefins. In comparison to the cinnamyl ether series, the reaction proceeded with similar yields and selectivities for either (*E*)- and (*Z*)-olefins (**3l**−**3r**). With (*E*)-olefins, the major isomer was the 1*R*, 2*R*, 3*R*; with (*Z*)-olefins, the major isomer was the 1*S*, 2*R*, 3*S* (for example, see **3l** vs **3m**) (confirmed by NOE). We determined that a 1,2-disubstituted alkene is a requirement for high diastereocontrol. The reaction of allyl benzyl ether yielded the corresponding borocyclopropane **3s** in a 75% yield and poor diastereoselectivity (1.5:1 dr), providing the *cis*

Scheme 1. Synthesis of Borocyclopropanes from Protected Allylic Alcohols





[a]Isolated yield of major diastereomer. [b]Combined isolated yield of both diastereomer. [c]Obtained from the corresponding -OBoc protected substrate (**2aa**).

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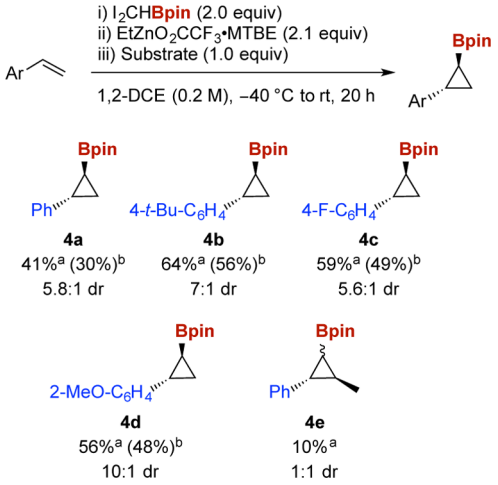
isomer as the major product. Similarly, the borocyclopropane **3t** was generated with 2.2:1 dr, favoring the *cis* isomer.

The reaction proceeds efficiently with silyl ethers. Various TBS-protected allylic alcohols were converted into the corresponding cyclopropane **3q**, **3r** and **3u**−**3x** in satisfying yields and diastereoselectivities.

The chemoselectivity of the reaction was successfully evaluated as well by cyclopropanating substrates bearing sensitive functional groups (**3y**−**3ac**).

The scope of the reaction was also extended to styrenes. Although the desired products could be obtained, the yields and the selectivities were not as high as the ones observed in the allylic ether series. The obtained *trans*-borocyclopropanes were found to be major diastereoisomers (Scheme 2). When *trans*-*β*-methylstyrene was submitted to the cyclopropanation conditions to generate **4e**, a significant drop in yield and selectivity was observed.

Scheme 2. Cyclopropanation of Styrenes



[a]Yield measured by ^{1}H NMR using triphenylmethane as internal standard. [b]Combined isolated yield of both isomers.

The observed diastereoselectivities are consistent with a transition state model in which minimization of steric interactions between the pinacolboron group and the R^1 and R^2 substituents plays a key role (Figure 1, **TS-1** vs **TS-2**). Coordination between the zinc center and the allylic ether oxygen is likely only occurring in the benzyl ether series. This model is also consistent with the lower diastereocontrol observed with allylic ethers, 1,1-disubstituted allylic ethers, and styrene derivative.

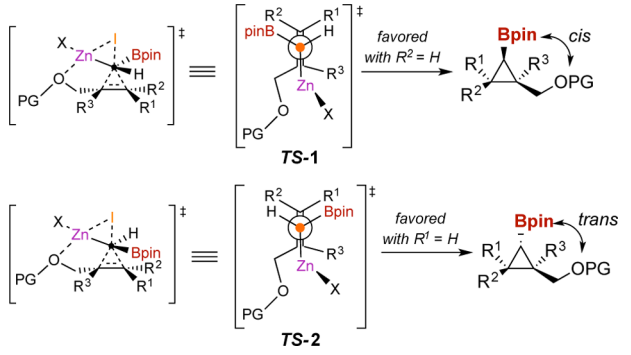
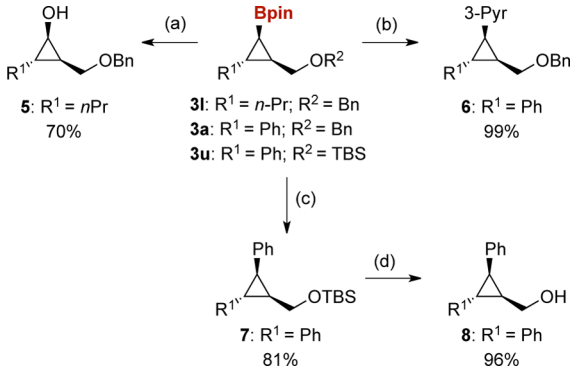


Figure 1. Proposed transition state model for the borocyclopropanation.

To illustrate the versatility of the highly substituted borocyclopropanes, we have carried out subsequent post-functionalizations to access 1,2,3-trisubstituted cyclopropanes.

Boronate **3l** was oxidized to the corresponding cyclopropanol **5** in the presence of H_2O_2 and NaOH in 70% yield. We could also achieve a Suzuki−Miyaura cross-coupling of **3a** with 3-bromopyridine as the coupling partner in 99% yield using $Pd(dba)_2/PCy_3$ in a biphasic toluene/KOH aqueous mixture. A second Suzuki−Miyaura coupling was achieved on boronate **3u** in 81% yield. The product of this reaction successively underwent TBAF-mediated deprotection of the TBS group to provide the free alcohol **8** in 96% yield (Scheme 3).

Scheme 3. Postfunctionalization of Borocyclopropane Derivatives



[a]H_2O_2 (30%, 2 equiv), NaOH (aq) (1 equiv), THF, 0 °C, 30 min.[10a] [b]$Pd(dba)_2$ (5 mol %), PCy_3 (10 mol %), 3-bromopyridine (2 equiv), KOH (3 N) (6 equiv), toluene, 115 °C, 20 h. [c]$Pd(dba)_2$ (7 mol %), PCy_3 (15 mol %), iodobenzene (2 equiv), KOH (3 N) (6 equiv), toluene, 115 °C, 20 h. [d]TBAF (1.2 equiv), THF, 0 °C to rt, 110 min.

In summary, we have developed a highly efficient borocyclopropanation using a novel boromethylzinc carbenoid. This reaction generally proceeds with good yields and selectivities with a wide range of alkenes. The product are versatile building blocks to access polysubstituted cyclopropane derivatives in a stereocontrolled fashion. Further work is in progress to expand this reaction into an enantioselective version.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09090.

Experimental procedures, compound characterization data, and NMR spectra for new compounds (PDF)
Data for $C_{23}H_{29}BO_3$ (CIF)
Data for $C_7H_{13}BI_2O_2$ (CIF)
Data for $C_{22}H_{37}BO_3Si$ (CIF)

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Notes

The authors declare no competing financial interest.

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