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A Modular Approach to the Synthesis of *gem*-Disubstituted Cyclopropanes

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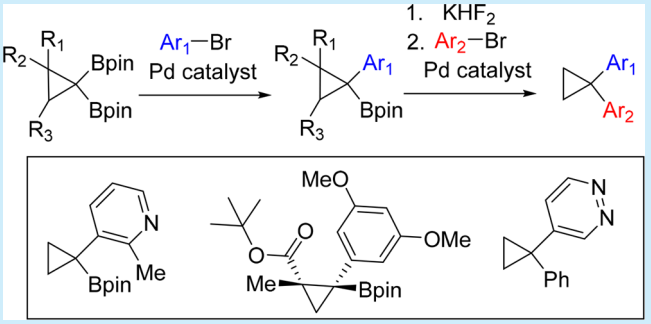
Supporting Information

ABSTRACT: A diastereoselective, Pd-catalyzed Suzuki−Miyaura coupling reaction of geminal bis(boryl)cyclopropanes has been developed. The reaction offers a highly modular approach to the synthesis of tertiary cyclopropylboronic esters. The resulting boronic esters may be further functionalized to afford a range of *gem*-disubstituted cyclopropanes, which represent an important structural motif in the pharmaceutical industry. Sequential Suzuki−Miyaura cross-coupling reactions of *gem*-bis(boryl)cyclopropanes are also reported. The coupling protocols are compatible with a broad range of functionalized aryl and heteroaryl bromides.



The cyclopropane moiety has been broadly utilized in structure-based drug design for over 50 years.[1] The incorporation of the cyclopropyl scaffold into drug molecules can improve metabolic stability,[2] attenuate pK_a[3] and lipophilicity,[4] and provide entropically favorable binding through conformational constraint.[5] Of particular interest to our group is the geminal disubstituted cyclopropane motif, which is present in a significant number of therapeutically relevant small molecules (Figure 1).[6,7] A sustained interest in the exploitation

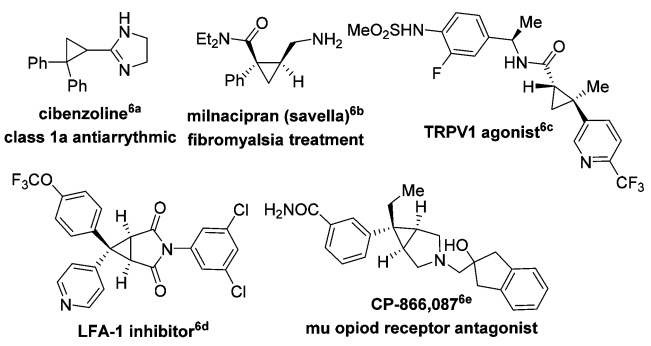


Figure 1. Selection of bioactive molecules containing the *gem*-disubstituted cyclopropane motif.

of *gem*-disubstituted cyclopropanes in drug discovery has spurred the development of elegant synthetic methods for their preparation.[8] However, the reported methods have limited potential for high-throughput chemistry: the need for prefunctionalized olefins and or diazo compounds poses a particular challenge to the rapid modification of the geminal substituents of the cyclopropane ring.

The reactivity of *gem*-bis(boryl)alkanes offers an attractive approach to the modular construction of *gem*-disubstituted cyclopropanes. Excellent chemoselectivity for engagement of a single boryl group is observed in a wide range of organic transformations involving *gem*-bis(boryl)alkanes,[9] allowing sequential modification of the boryl groups.[10] For example, Shibata and co-workers developed an iterative Suzuki−Miyaura coupling (SMC) reaction of *gem*-bis(boryl)alkanes (Scheme 1a).[11] More recently, Morken and co-workers disclosed a diastereoselective protocol for the synthesis of a *gem*-disubstituted cyclopropane by deborylative alkylation (Scheme 1b).[12]

Inspired by the work of Shibata and Morken, we reasoned that sequential SMC reactions of *gem*-bis(boryl)cyclopropanes would provide a robust protocol for the modular synthesis of *gem*-disubstituted cyclopropanes (Scheme 1c). While the SMC reaction of primary *gem*-bis(boryl)alkanes has been well documented,[13] the analogous reaction of a secondary *gem*-bis(boryl)alkane has no precedent. The added steric bulk from substitution of the reactive carbon of a boron species results in sluggish transmetalation and facile protodeborylation.[14,15] To achieve our goal of limiting the undesired reactivity associated with a bulkier alkylboron species, we chose the simple, unsubstituted *gem*-bis(boryl)cyclopropane **1a** as our model substrate in the SMC reaction.

An efficient synthesis of our model substrate **1a** was accomplished in a single step from commercially available cyclopropyl bromide (Scheme 2).[16,17] Generation of the cyclopropyl lithioate described by Whitby[18] and quenching with bis(pinacolato)diboron afforded the desired material. No decomposition of the *gem*-bis(boryl)cyclopropane **1a** was observed upon storage at room temperature for up to 10 months.

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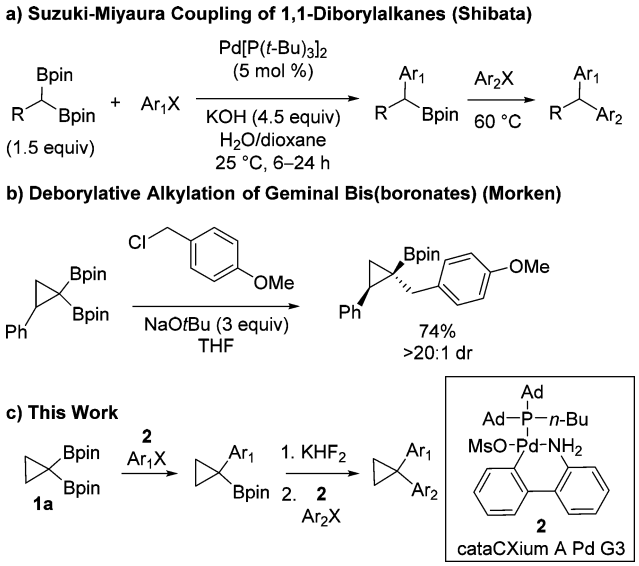
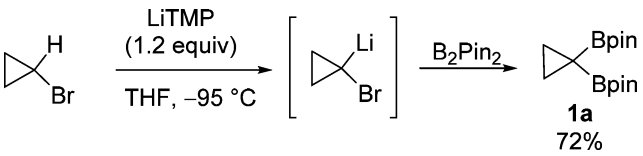
Scheme 1. Reactivity of Geminal Bis(boryl)alkanes and Proposed Synthetic Route to *gem*-Diarylcyclopropanes

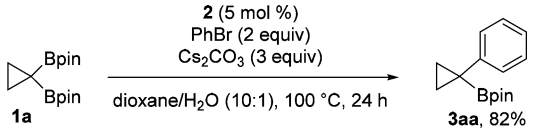


Scheme 2. Preparation of 1,1-Bis[(pinacolato)boryl]cyclopropane (1a)



Our investigation of the Suzuki–Miyaura cross-coupling reaction of the model substrate **1a** began with an evaluation of the reaction conditions (Table 1). We determined that cataCXium A Pd G3 in the presence of cesium carbonate catalyzes the cross-coupling of **1a** with bromobenzene in excellent yield. The precatalyst $PdCl_2$(dppf) may be used without significant impact on product distribution, but the use of other catalysts resulted in lower yields of **3aa** (entries 1 and 2). The best results were obtained when the reaction was performed at 100 °C; incomplete conversion of **1a** was observed at lower temperatures (entries 3 and 4). A dioxane–water solvent mixture provided optimal results in the SMC reaction, while anhydrous conditions and other solvents decreased the yield of desired product **3aa** (entries 5 and 6). When cesium fluoride or a stronger base was employed, near-quantitative conversion to protodeborylation side products was observed (entries 7–9). The desired product was obtained in good yields when bromobenzene was used as the limiting reagent or equimolar to **1a** (entries 10 and 11). The reaction is scalable; **3aa** was isolated in 64% yield on gram scale (entry 11).[19]

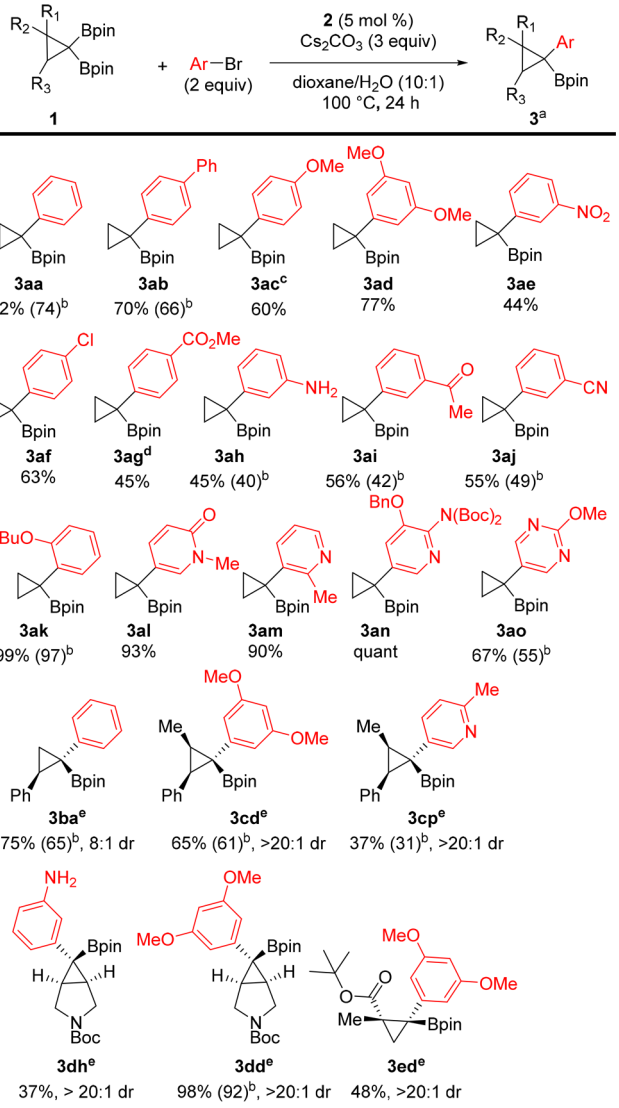
Table 1. Reaction Optimization



entry	deviation from "standard conditions"	yield (%)[a]
1	$PdCl_2$(dppf) (5 mol %)	77
2	XPhos Pd G 2 (5 mol %)	47
3	reaction performed at 50 °C	14
4	reaction performed at 75 °C	52
5	dioxane (anhydrous)	<2
6	toluene/H_2O (10:1)	47
7	CsF (3 equiv)	<2
8	KOH (8 M in H_2O, 3 equiv), 25 °C	7
9	KOH (8 M in H_2O, 3 equiv), 100 °C	<2
10	1 equiv of PhBr and 2 equiv of **1a**	74
11	1 equiv of PhBr and 1 equiv of **1a**	77
12	reaction performed on 7.48 mmol scale	64[b]

[a]Yield determined by ^{1}H NMR based on comparison with $PhSiMe_3$ as internal standard. [b]Isolated yield.

Scheme 3. Scope of the Suzuki–Miyaura Coupling Reaction



[a]Yield determined by ^{1}H NMR based on comparison with $PhSiMe_3$ as internal standard. [b]Isolated yield. [c]Reaction performed with $PdCl_2$(dppf) instead of cataCXium A Pd G3. [d]Reaction was stopped after 4 h. [e]Reaction performed at 110 °C.

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tolerated under the reaction conditions.[20] Electron-rich arenes with substituents in the *ortho*-, *meta*-, and *para*-positions were well tolerated, affording the desired products in good yields (**3ac**, **3ad**, and **3ak**, respectively). The transformation was compatible with a variety of reactive functional groups, including NO_2 (**3ae**), Cl (**3af**), CO_2Me (**3ag**), NH_2 (**3ah**), C(O)Me (**3ai**), and CN (**3aj**). When aryl bromides containing strongly electron-withdrawing substituents at the para position were coupled, complete protodeborylation of the desired tertiary boronic ester was observed (e.g., **3ag**). Fortunately, the yield of **3ag** was recovered when the reaction was stopped after 4 h. We were also pleased to find that heterocyclic bromides [i.e., pyrimidone (**3al**), substituted pyridines (**3am** and **3an**), and pyrimidine (**3ao**)] underwent smooth cross-coupling to furnish the desired boronic esters in excellent yields.

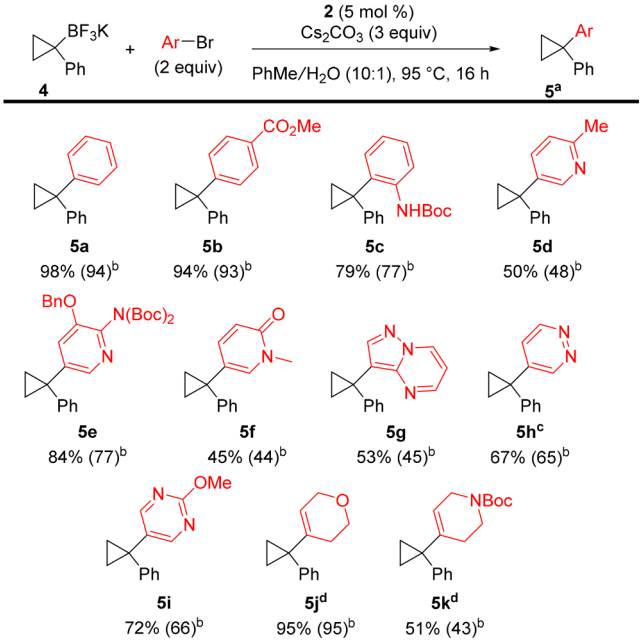
The coupling of substituted *gem*-bis(boryl)cyclopropanes resulted in a highly diastereoselective transformation (**3ba**).[21] A single diastereomer was observed for *cis*-disubstituted cyclopropanes (**3cd** and **3cP**). The SMC procedure was applied to the biologically relevant azabicyclo[3.1.0]hexane ring system to afford single diastereomers of the corresponding Bpin reagents (**3dh** and **3dd**). We observed a directing group effect for the ester-substituted cyclopropane **3ed**, where transmetalation occurred exclusively at the Bpin group that was *cis* to the ester.[22]

With a robust protocol for the synthesis of tertiary boronic esters in hand, we planned a straightforward route to the construction of *gem*-diarylcyclopropanes by sequential SMC reactions. The transition-metal-mediated cross-coupling reaction of a tertiary cyclopropyl boron species[23] is challenging and has precedents only in activated systems or in radical-mediated alkyl transfer reactions.[24] Guided by our previous work in the cross-coupling of tertiary trifluoroborates of 3-azabicyclo-[3.1.0]hexanes,[24b] we chose to convert **3aa** to the tertiary trifluoroborate **4** to enable the subsequent cross-coupling reaction (Scheme 4).[25,26] A reaction of **4** with bromobenzene proceeded in excellent yield to afford the desired *gem*-diphenylcyclopropane **5a**. The reaction was tolerant of ester (**5b**) and *ortho*-substituted Boc protected aniline (**5c**) functional groups. A broad range of heterocyclic bromides were coupled in good yields, including substituted pyridines (**5d** and **5e**), pyridone (**5f**), pyrazolo[1,5-*a*]pyrimidine (**5g**), pyridazine (**5h**), and pyrimidine (**5i**). Vinyl triflates could also be employed as coupling partners, providing access to pyran (**5j**) and piperidine (**5k**) scaffolds.

To demonstrate further the synthetic utility of the tertiary boronic esters generated by our SMC protocol, we carried out derivatizations to afford a wide array of *gem*-disubstituted cyclopropanes containing a diverse set of functional groups (Scheme 5).[27] Amination of **4** proceeded in excellent yield under conditions reported by Aggarwal (**6**).[28] Upon exposure to a mild oxidant, **3ab** was readily converted to the corresponding alcohol **7**.[29] Illustrative examples of homologation reactions are also shown in Scheme 3, which provided access to propenyl (**8**),[30] vinyl (**9**),[31] and ketone (**10**)[32] functional groups.

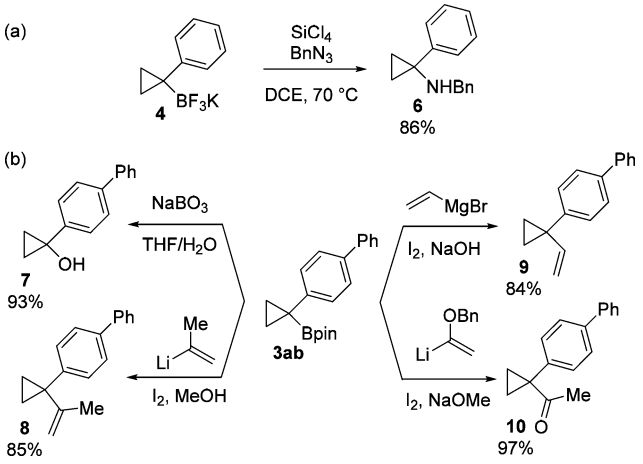
In summary, we developed a highly efficient and modular protocol for the synthesis of *gem*-diarylcyclopropanes. The reaction proceeded in moderate to excellent yields and high diastereoselectivity for a broad range of aryl bromides and substituted *gem*-bis(boryl)cyclopropanes. The synthetic utility of the tertiary boronic ester products was demonstrated by further derivatization to other functional groups. A slight modification of the SMC protocol allowed the coupling of tertiary trifluoroborate **4**, providing access to a wide array of *gem*-diarylcyclopropanes containing diverse functional groups and heterocycles. We believe the presented transformations will be of particular interest in the context of accelerating drug discovery programs due to the modularity afforded by the *gem*-bis(boryl)cyclopropanes and mild reaction conditions of the SMC procedures. Research on further applications for *gem*-bis(boryl)cyclopropanes is ongoing in our laboratory.

Scheme 4. Suzuki–Miyaura Coupling Reaction of Tertiary Trifluoroborate 4



[a]Yield determined by ^{1}H NMR based on comparison with $PhSiMe_3$ as internal standard. [b]Isolated yield. [c]Prepared from the HBr salt of 4-bromopyridazine. [d]Prepared from the corresponding vinyl triflate.

Scheme 5. Synthesis of *gem*-Disubstituted Cyclopropanes by Derivatization of Tertiary Boron Species 4 and 3ab



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■ ASSOCIATED CONTENT

Supporting Information

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Full experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(19) Gram scale preparations of **3ab** and **3an** were also performed. See the Supporting Information for additional details.
(20) Protodeborylation of the tertiary boronic esters is the major byproduct and contaminant of the coupling reaction and was observed to also occur during the workup and purification of the substituted *gem*-bis(boryl)cyclopropanes. For best results, aqueous workups were avoided and silica was pretreated with a solution of 0.5% triethylamine in heptane. See the Supporting Information for additional details.
(21) All stereochemical assignments are based on NOE correlations.
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