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Hydrogenation of Borylated Arenes

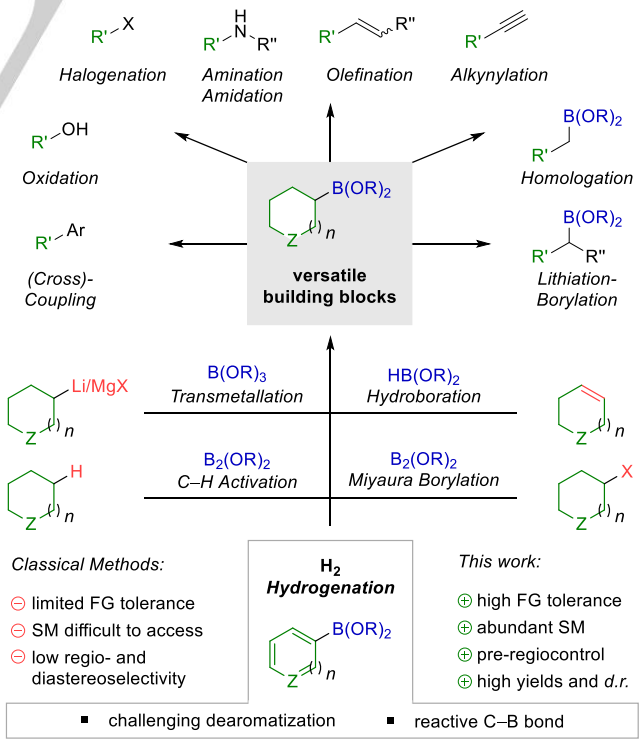
Marco Wollenburg[+], Daniel Moock[+], and Frank Glorius*

Dedicated to Prof. Bernt Krebs on the occasion of his 80th birthday

Abstract: The *cis*-selective Rh–CAAC catalyzed hydrogenation of abundant aryl boronic acids and their derivatives is reported. The reaction tolerates a variety of boron protecting groups and provides direct access to a broad scope of saturated, borylated carbo- and heterocycles with various functional groups. The transformation is strategically important as the versatile saturated boronate products are difficult to prepare by other methods. The utility of saturated cyclic building blocks was demonstrated by postfunctionalization of the boron group.

Alkyl boronic acid derivatives have emerged as an important class of intermediates with broad utility in the fields of modern organic synthesis, medicine and material science. Particularly, alkylboronate esters are versatile building blocks that can be derivatized to C–halogen, C–heteroatom, and C–C bonds.[1] This can be achieved by single-step deborylative nucleophilic addition, 1,2-metallate rearrangement[2] and transition-metal catalyzed cross-coupling reactions of C(sp^3) organometallics with electrophiles.[3] Cycloalkyl boronates can thus serve as important intermediates for the stereoselective preparation and post-functionalization of a wide range of valuable carbo- and heterocycles (Scheme 1).[1,2] However, the widespread utilization of cyclic alkylboron compounds is frequently hindered by their challenging synthesis. Classical approaches mainly focus on the synthesis of non-cyclic derivatives, which have a number of challenges and limitations associated with them for the construction of cyclic systems. For example, the transmetallation[4] from alkyl lithium or alkyl magnesium reagents with boron electrophiles suffers from functional group incompatibility. The hydroboration of olefins[5] is limited by the accessibility of the corresponding starting material and the generation of regioisomers for such internal olefins. The transition-metal catalyzed borylation of C(sp^3)–H bonds developed by Hartwig and others uses abundant aliphatic cycles, however it is limited to relatively simple substrates due to the high number of potentially reactive C–H bonds.[6] More recently, the Miyaura-type borylation of alkyl halides emerged as an option to access alkyl boronates.[7] However, this method is restricted by the accessibility of the corresponding alkyl halides and a narrow scope. In 2017, Li, Baran, and Aggarwal reported elegant methods for the synthesis of alkyl boronic acid derivatives by decarboxylative borylation of pre-activated carboxylic acids.[8] A more general approach for the synthesis of borylated carbocycles is the concept of borylative cyclization, although prefunctionalized substrates are again required.[9]

Whilst many borylation strategies have been developed, exploration of conceptually distinct approaches to form cyclic alkylboron compounds with predictable stereo- and regiocontrol remains desirable. A straightforward approach to solve this synthetic problem is through arene hydrogenation. Hydrogenation of arenes has emerged as a powerful strategy to construct a variety of three-dimensional cyclic products from readily available planar compounds.[10] Other than the typical challenges associated with dearomatization, functional group tolerance remains a major limitation. Encouraged by the reports on the Rh–CAAC (cyclic (alkyl)(amino)carbene) catalyzed chemoselective hydrogenation of aromatic ketones by Zeng,[11] as well as fluoroarenes and silylated arenes by our group,[12] we sought to expand the scope of the chemoselective arene hydrogenation. It should be noted that Bullock et al. showed in a recent study that nanoparticles are the active catalyst of an arene hydrogenation utilizing a Rh–CAAC complex. The heterogeneous nature of this catalyst, which was confirmed by various mechanistic and spectroscopic experiments, is likely crucial to both the reactivity and selectivity of this system.[13] To date, the hydrogenation of borylated arenes has been underexplored.[12,14] Given the synthetic value of organoboron compounds and the fact that no general method for the construction of borylated carbo- and heterocycles is known, we believed a thorough synthetic study was required.



Scheme 1. Application of cyclic alkyl boronic acid derivatives and general approaches towards their synthesis. SM = starting material; FG = functional group; Z = CH/CH_2, heteroatom; X = halide, *n* = 0, 1.

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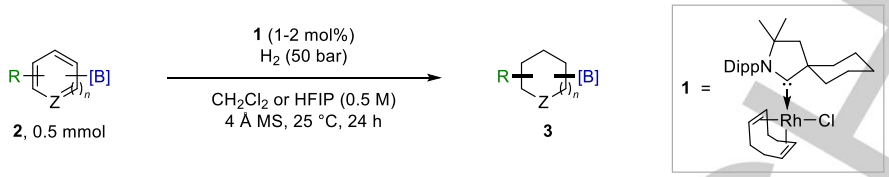
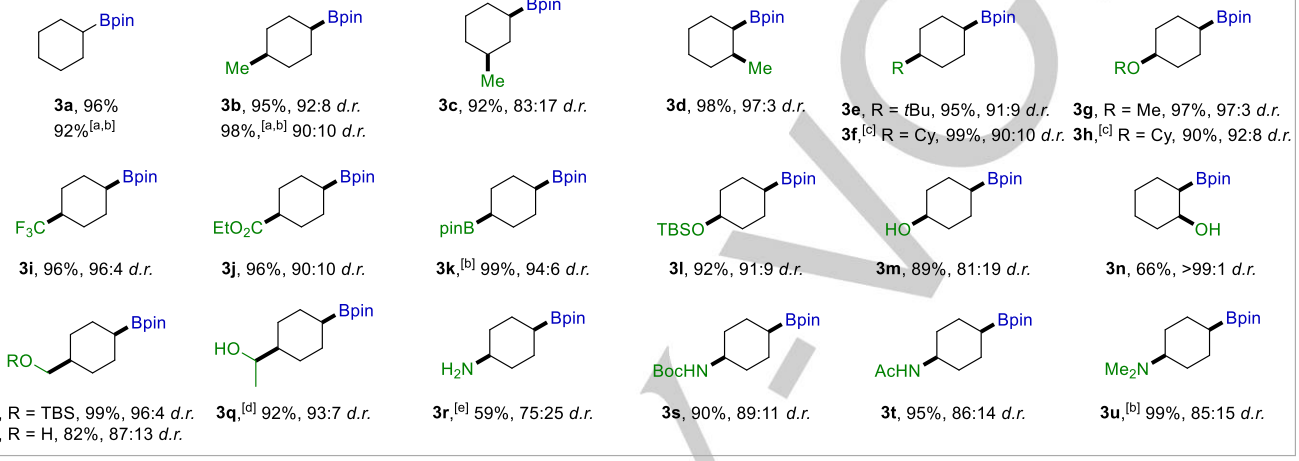
Herein we report the first comprehensive study to access cyclic, C(sp^3)–B substituted compounds from abundant arylboronic acid precursors in a step-economical and diastereoselective fashion, tolerating a broad variety of functional groups.



Various FG



3a, 96%
92%[a,b]

3b, 95%, 92:8 *d.r.*
98%,[a,b] 90:10 *d.r.*

3c, 92%, 83:17 *d.r.*

3d, 98%, 97:3 *d.r.*

3e, R = *t*Bu, 95%, 91:9 *d.r.*
3f,[c] R = Cy, 99%, 90:10 *d.r.*

3g, R = Me, 97%, 97:3 *d.r.*
3h,[c] R = Cy, 90%, 92:8 *d.r.*

3i, 96%, 96:4 *d.r.*

3j, 96%, 90:10 *d.r.*

3k,[b] 99%, 94:6 *d.r.*

3l, 92%, 91:9 *d.r.*

3m, 89%, 81:19 *d.r.*

3n, 66%, >99:1 *d.r.*

3o, R = TBS, 99%, 96:4 *d.r.*
3p, R = H, 82%, 87:13 *d.r.*

3q,[d] 92%, 93:7 *d.r.*

3r,[e] 59%, 75:25 *d.r.*

3s, 90%, 89:11 *d.r.*

3t, 95%, 86:14 *d.r.*

3u,[b] 99%, 85:15 *d.r.*

Multisubstituted

3v,[c] 99%, 96:4 *d.r.*

3w,[c] X = CH_2, 96%, 97:3 *d.r.*
3x,[f] X = O, 95%, 95:5 *d.r.*

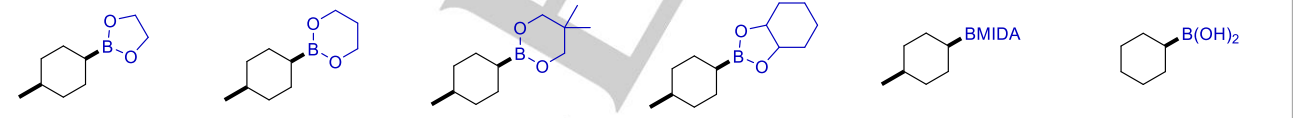
3y,[b,e] 88%, >99:1 *d.r.*

3z, 53%, 96:4 *d.r.*

3aa, 96%, 98:2 *d.r.*

3ab,[b] 94%, 96:4 *d.r.*

Boron group variation



3ac, 99%, 90:10 *d.r.*

3ad, 99%, 94:6 *d.r.*

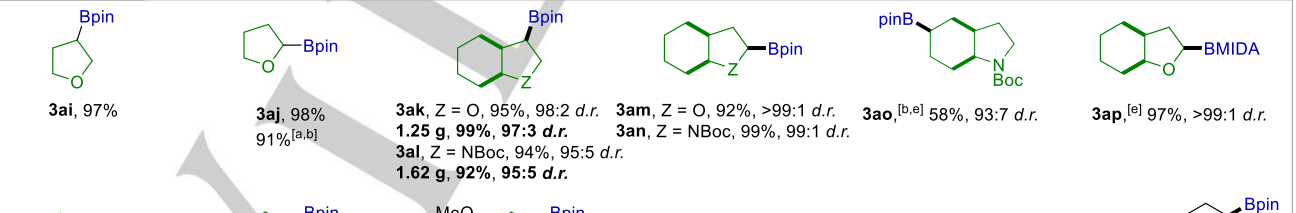
3ae, 99%, 90:10 *d.r.*

3af,[c] 99%, 88:12 *d.r.*

3ag,[e] 97%, 80:20 *d.r.*[g]

3ah,[b] 69%

Heterocycles



3ai, 97%

3aj, 98%
91%[a,b]

3ak, Z = O, 95%, 98:2 *d.r.*
1.25 g, 99%, 97:3 *d.r.*
3al, Z = NBoc, 94%, 95:5 *d.r.*
1.62 g, 92%, 95:5 *d.r.*

3am, Z = O, 92%, >99:1 *d.r.*
3an, Z = NBoc, 99%, 99:1 *d.r.*

3ao,[b,e] 58%, 93:7 *d.r.*

3ap,[e] 97%, >99:1 *d.r.*

3aq, 99%

3ar, 63% (75%)[h]

3as,[b,e] 37%, >99:1 *d.r.*

3at, 70%, 57%[a,b]
1.37 g, 88%

3au, 75%, 97:3 *d.r.*

3av,[b,c,e] 92%, 84:16 *d.r.*

Scheme 2. Substrate scope for the hydrogenation of borylated arenes. Isolated yields after column chromatography. The *d.r.* values were determined by GC-MS prior to purification. Piperidines were trapped with Boc_2O prior to isolation. Dipp = 2,6-Di*iso*propylphenyl, pin = pinacolato, TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl, Ac = acetyl. For details, see Supporting Information. [a] Free boronic acid as starting material. [b] 40 °C. [c] Hydrogenation of both aromatic rings. [d] Full hydrogenation of the aromatic ring and the carbonyl group. [e] 3 mol% catalyst loading. [f] Benzo-1,4-dioxane derivative as substrate. [g] The *d.r.* value was determined by ^{1}H NMR. [h] 2-Methoxy-5-pyridineboronic acid pinacol ester as substrate.

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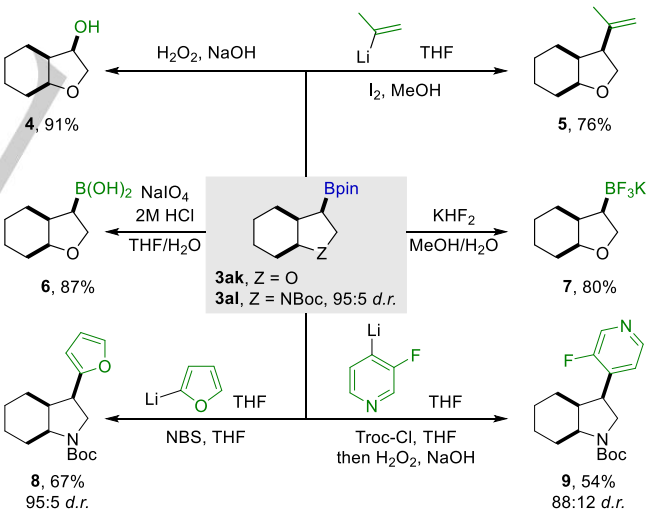
We commenced our studies by investigating the hydrogenation of free phenyl boronic acid to cyclohexylboronic acid with Rh–CAAC[15] complex **1**.[11-13] To the best of our knowledge, there was previously no method available to hydrogenate vinyl and benzene boronic acids. However, the isolation of free aliphatic boronic acids is generally tedious and nontrivial, which hindered reaction optimization. To circumvent this issue, optimization studies were then conducted using OTBS–substituted phenylboronic acid pinacol ester **2l**, which was more convenient to handle. These studies showed that conditions using CH_2Cl_2, crushed 4 Å molecular sieves (MS), and 50 bar of H_2 were optimal.[16]

With the optimized conditions in hand, we began scoping studies with different boronic acids and esters (Scheme 2). The hydrogenation of simple arenes, bearing aliphatic substituents (**2a**–**f**), provided the corresponding carbocycles in excellent yields. The reaction also proceeded with sterically demanding substituents, such as *tert*-butyl (**3e**) and cyclohexyl groups (**3f**) in high yields and diastereomeric ratio (*d.r.*). Electron donating ether as well as electron withdrawing trifluoromethyl and ester substituents were well tolerated (**3g**–**j**). Protected alcohols (**2l**, **2o**) smoothly underwent hydrogenation to the saturated products. More interestingly, unprotected phenols **2m** and **2n**, as well as benzyl alcohol **2p** could be reduced in good yields. We were intrigued by the fact, that even unprotected aniline boronate ester **2r** could be hydrogenated by changing the solvent from CH_2Cl_2 to hexafluoroisopropanol (HFIP). Additionally, Boc and acetyl protected amines (**3s**, **3t**) could be obtained in high yields. The *cis*-selectivity of the hydrogenation was confirmed by X-ray diffraction analysis of products **3s** and **3ak**. The highly valuable Bpin group in combination with preserved (protected) alcohols and amines offers a new avenue to functionalize cyclohexyl derivatives. Next, we turned our attention to polycyclic and heterocyclic substrates. Different naphthalene derivatives were fully hydrogenated to the corresponding borylated *cis*-decalins (**3v**, **3w**). Various boron protecting groups were tested under the established conditions. Ethylene, propylene, and neopentyl glycol protected *para*-tolyl boronic acids **2ac**–**ae** were fully hydrogenated and isolated in quantitative yield. The corresponding catechol derivative **2af** was completely reduced under the conditions employed. By switching the solvent from CH_2Cl_2 to protic HFIP, the hydrogenation of methyliminodiacetic acid (MIDA) protected substrates (**2ag**, **2am**) was enabled. The hydrogenation of free phenylboronic acid **2ah** provided access to the saturated cyclohexylboronic acid. Thus, our developed method provides access to alkyl boronic acid derivatives with various boron protecting groups, which can influence the rate of transmetalation in cross-coupling reactions.[17] Since saturated heterocycles are an important structural motif, we extended the scope of the hydrogenation to different heteroarenes (**2ai**–**2av**). By hydrogenating indole derivatives **2al**, **2an** and **2ao**, access to the interesting *cis*-perhydroindole motif with further potential for functionalization was granted. Gram-scale hydrogenation of benzofuran **2ak** and indole **2al** was conducted, providing the perhydro products **3ak** and **3al** in very high yields. Moreover, also pyridines could be hydrogenated by our method, enabling access to an important class of borylated piperidines (**3ar**–**av**) with potential for application in drug design and subsequent boron group functionalization. Interestingly, undesired deborylation could be observed as a major side reaction, when hydrogenating 3-Bpin-substituted pyridines (**2ar**, **2as**). Comparing various alcoholic solvents, the unwanted deborylation was best suppressed in HFIP, furnishing 3-Bpin-substituted piperidine (**3ar**) in 63% yield. The yield could be increased to 75% by employing 2-methoxyl-5-pyridineboronic acid pinacol ester, which was hydrogenated with complete demethoxylation in the 2-position and no observable deborylation. Additionally, no deborylation was detected when employing 4-substituted pyridines (**2at**–**av**) as substrates. The hydrogenation of 4-Bpin pyridine was scaled up to gram-scale, providing access to a valuable borylated piperidine from an easily accessible starting material. In many cases, the major diastereomer could be separated by column chromatography, providing access to diastereomerically pure alkyl boronates with a very broad variety of functional groups. We also evaluated different heterogeneous hydrogenation catalysts for various scope examples in the course of this project. However, the employed Rh–CAAC complex **1**, proved to be the most effective in terms of both yield and diastereoselectivity (see Supporting Information, Figure S2). Inspired by the study of Bullock et al., revealing the active catalyst as nanoparticles, we performed initial mechanistic experiments, which are consistent with a heterogeneous system (see Supporting Information).[13]

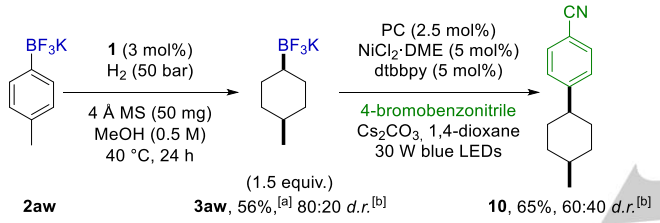
Having established an efficient and versatile method to access cyclic alkyl boronic esters, we sought to demonstrate their synthetic utility (Scheme 3).



Scheme 3. Functionalization of products. The *d.r.* values were determined by GC-MS prior to purification. THF = tetrahydrofuran, NBS = *N*-bromosuccinimide. Troc–Cl = 2,2,2-trichloroethyl chloroformate.

Oxidation of hydrogenated benzofuran derivative **3ak** by treatment with aqueous hydrogen peroxide afforded alcohol **4** in 91% yield. Alkenylation provided olefin **5** as a single diastereomer in 76% yield.[18] Deprotection of pinacol esters by treatment with sodium periodate furnished the corresponding

alkylboronic acids, synthetically valuable alternatives to the corresponding esters. Moreover, alkylboronic acids are of interest in pharmaceutical science as borono-bioisosters of carboxylic acids.[19] Treatment with KHF_2 converted alkyl boronate ester **3ak** to the corresponding organotrifluoroborate **7**. The stereospecific coupling of 3-borylated perhydroindole derivative **3al** with lithiated furan and 3-fluoropyridine was performed in order to demonstrate the synthetic utility of the obtained products.[20] However, the coupling with lithiated 3-fluoropyridine resulted in a slight erosion of the *d.r.* Organotrifluoroborates can serve as versatile reagents in transition-metal catalyzed and photoredox cross-coupling reactions.[21] Finally, we were intrigued to observe that aryl organotrifluoroborates could directly be converted to their saturated analogues by our protocol (Scheme 4). Hydrogenation of aryltrifluoroborate **2aw** at elevated temperature in methanol followed by filtration provided the crude alkyl trifluoroborate, which was directly used in a cross-coupling reaction with an aryl bromide, mediated by dual iridium and nickel catalysis.[21c]



Scheme 4. Hydrogenation of aryltrifluoroborates and photocatalytic transformation. Photocatalyst (PC) = $[Ir(dFCF_3ppy)_2bpy][PF_6]$, DME = dimethoxyethane, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl. [a] The product contained traces of an unknown impurity. [b] The *d.r.* value was determined by ^1H NMR.

In conclusion, we have developed a straightforward method to access borylated carbo- and heterocycles from readily available aryl boronic acids and their derivatives by Rh–CAAC catalyzed[13] arene hydrogenation. The cyclic alkylboron building blocks, which were previously difficult to access, were generally obtained in very high yields, with high diastereoselectivity and tolerating a broad variety of functional groups. Overall, we hope that this approach and the products described herein, will be widely used to enable a number of material science, drug design and agrochemical applications.

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Conflict of interests

The authors declare no conflict of interest.

Keywords: arene hydrogenation • boronic esters • cycloalkanes • heterocycles • building blocks

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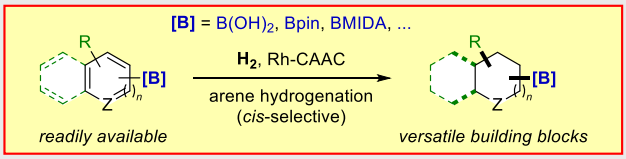

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Hydrogenation of Borylated Arenes

Not flat anymore: The *cis*-selective Rh–CAAC catalyzed hydrogenation of abundant aryl boronic acids and their derivatives is reported. The reaction tolerates a variety of boron protecting groups and provides direct access to a broad range of saturated, borylated carbo- and heterocycles with various functional groups. The utility of these saturated cyclic building blocks was demonstrated by postfunctionalization of the boron group.