Synthesis of Multi-Substituted Bicycloalkyl Boronates: An Intramolecular Coupling Approach to Alkyl Bioisosteres

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Bicyclic hydrocarbons, bicyclo[1.1.1]pentanes (BCPs) in particular, play an emerging role as saturated bioisosteres in pharmaceutical, agrochemical, and material chemistry. Taking advantage of strain release strategies, prior synthetic studies have featured the synthesis of bridgehead-substituted (C1, C3) BCPs from [1.1.1]propellane. This work describes a novel approach to accessing multi-substituted BCPs via a new type of intramolecular cyclization. In addition to the C1, C3-disubstituted BCPs, this method also enables the construction of yet underexplored multi-substituted (C1, C2 and C3) BCPs from readily accessible cyclobutanones. Also, the broad generality of this method is examined through synthesis of a variety of other caged bicyclic molecules, ranging from [2.1.1] to [3.2.1] scaffolds. The modularity afforded by the pendant bridgehead Bpin resulted from the cyclization is demonstrated via several downstream functionalizations, highlighting the ability of this approach for programmed and divergent synthesis of multi-substituted bicyclic hydrocarbons.

Caged bicyclic molecules that exhibit considerable ring strain have long been the subject of intense study due to their unusual geometries, physical properties and theoretical interest[1]. Recent developments in medicinal chemistry shine a new light on the potential utility of these C(sp^3)-rich hydrocarbons[2]. Owing to their unique physical and chemical properties, bicyclic hydrocarbons exhibit the ability to modulate the pharmacokinetic and physiochemical properties of drug candidates[3]. Bicyclo[1.1.1]pentanes (BCPs) containing substitutions at bridgehead positions (C1, C3) are now widely recognized as saturated bioisosteres for *para*-substituted benzenes[4]. Analogously, related caged scaffolds with differentiated substitutions (Figure 1A) are expected to be ideal bioisosteres of *ortho*- or *meta*- substituted benzenes[5,6]. Currently BCPs are synthesized from the highly strained [1.1.1]propellane (**6**) (the strain energy of the C–C bond = ~59~65 kcal/mol)[7-9], using methodologies pioneered by Wiberg[7], Michl[10], Baran[11], and others[12-20], wherein **6** is transformed to symmetric and asymmetric BCPs using either single- or two-electron transfer pathways (Figure 1B). These efforts have primarily focused on accessing C1 and/or C3-substituted BCPs until two recent reports[21,22] disclosed strategies for the systematic functionalization of the backbone (C2) of BCPs. In addition to strain-release, Wurtz

coupling[23], Norrish–Yang cyclization[24], [2+2] photo-cycloaddition[25], ring expansion[26], and ring contraction[27] represent other means to access BCPs. However, these methods are often plagued by low yields or limited substrate scope. In light of the aforementioned issues, practical and efficient methodologies to construct multi-substituted (C1/C2/C3) BCPs **8** are highly desirable as they represent elusive bioisosteres of ortho-/meta-substituted benzene rings and would enable access to novel chemical space. Herein we describe a novel approach for the construction of multi-substituted BCPs via the intramolecular coupling of cyclobutane-tethered sulfonyl hydrazones and boronic esters. This intramolecular cyclization strategy not only provides a general and operationally simple method for the synthesis of BCPs but can also be expanded to access a wide range of bicyclic alkyl boronates, all of which have the potential to serve as useful benzene bioisosteres. Additionally, the pendant bridgehead alkyl boronate allows for subsequent downstream functionalizations, resulting in a modular and programmable template for the construction of multi-substituted caged bicyclic molecules.

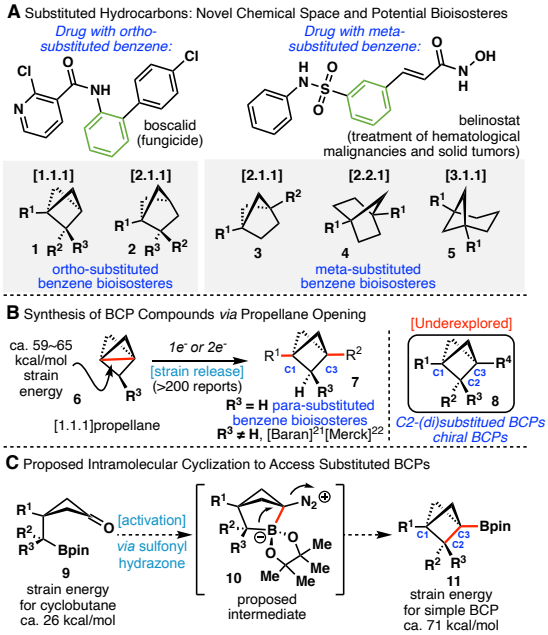
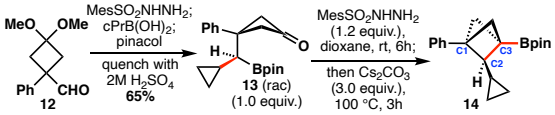


Figure 1. Bridged Hydrocarbons and BCPs Syntheses. (**A**) Substituted hydrocarbons provide novel chemical space as potential bioisosteres; (**B**) The state-of-art for BCP synthesis using strain releasing strategy; (**C**) Proposed intramolecular cyclization to access strained multi-substituted BCPs from cyclobutanone.



entry	deviation from above (**13** to **14**)	yield (%)[a,b]
1	none	88 (83)
2	$TsNHNH_2$ in place of $MesSO_2NHNH_2$	63
3	$TrisylNHNH_2$ in place of $MesSO_2NHNH_2$	67
4	K_2CO_3 in place of Cs_2CO_3	26
5	KO*t*Bu in place of Cs_2CO_3	18
6	PhCl in place of dioxane	78
7	DMF in place of dioxane	52
8	reaction performed at 80 °C	78
9	reaction performed at 110 °C	75
10	stirred open to air	77

[a]Yield determined by GC analysis with trimethoxybenzene as an internal standard; [b] Yield in parenthesis is isolated yield; Mes = mesityl; cPr = cyclopropyl; Ts = tosyl; Trisyl = triisopropylbenzenesulfonyl.

Figure 2. Cyclization Optimization to Access BCPs

Our retrosynthetic analysis to multi-substituted BCPs (strain energy ~71 kcal/mol) relies on cyclization from cyclobutanones **9** (strain energy for cyclobutane ~26 kcal/mol)[28]. However, previous studies indicated that base-initiated intramolecular substitution proved unsuccessful in BCP formation[29], presumably due to the unusual strain energy present in the desired target. Taking inspiration from our[30] and other's prior studies[31-35] on base-promoted cross-coupling between alkyl sulfonylhydrazones and boronic acids, we surmised that base-mediated intramolecular coupling of cyclobutane-tethered sulfonyl hydrazones and boronates might enable the formation of a high energy bicyclic [2.1.1] zwitterionic intermediate **10**. Furthermore, we hypothesized that this high-energy intermediate might undergo subsequent 1,2-metallate rearrangement to form BCP **11** via extrusion of N_2. While the C–B bond in **10** is not perfectly aligned with the leaving group, the loss of N_2 could help drive the subsequent 1,2-metallate rearrangement and contraction to the desired BCP scaffold **11**.[36,37] Aryl and

alkyl boron pinacol esters (Bpin) have *a priori* been reported as recalcitrant coupling partners in Barluenga-Valdés coupling[31] and its modifications.[30] However, from a both practicality and ease of access perspective, alkyl Bpins were identified as ideal starting materials. Additionally, we envisioned that the short spatial distance between the tethered coupling partners might help overcome the poor reactivity of the Bpin, thereby enabling the intramolecular cyclization to occur. To test this theory, the key intermediate **13** was prepared in one-step using our boron-preserving cross-coupling conditions from cyclobutane aldehyde **12** (Figure 2, see SI for more details)[30]. Subjecting **13** to *in situ* hydrazone formation followed by our previously reported conditions for intermolecular cross-coupling, gratifyingly afforded the desired bridgehead Bpin substituted BCP product **14** in 78% yield (Entry 6). Subsequent optimization of sulfonylhydrazide, base, solvent and temperature (summarized in Figure 2; see SI for additional information) resulted in the identification of optimal conditions, employing mesitylsulfonyl hydrazide, cesium carbonate and dioxane to afford the coupling product **14** in 83% isolated yield (88% GC yield) (Entry 1). The use of mesitylsulfonyl hydrazide as the activation reagent was found to be the key for effecting efficient hydrazone condensation and *in situ* generation of the diazo intermediate (Entries 2 and 3, starting material **13** is left for these two cases). The selection of base (Entries 4 and 5) and solvent (Entries 6 and 7) were also important for obtaining high yield for this cyclization. Varying the temperatures also afforded the desired product **14** (Entries 8 and 9), albeit in lower yields. It is noteworthy that the reaction does not require inert atmosphere and proceeds smoothly under air, presumably due to the improved stability of the Bpin motif in comparison to its $B(OH)_2$ counterpart (Entry 10).

With the optimal conditions in hand, the substrate scope of this intramolecular cyclization to access di-, tri-, and tetra-substituted BCPs was systematically investigated (Figure 3). With the hypothesis that this cyclization would be influenced by the conformation of cyclobutane **9**, our exploration commenced with a sterically large phenyl group (A value = 3.0) on cyclobutane ring[38]. The cyclobutanone Bpins **9** were prepared from the corresponding aldehydes, ketones, esters and halides (see SI for detailed synthetic information)[39-44]. A primary alkyl Bpin (R_2 = H, R_3 = H) underwent smooth cyclization to the C1, C3 disubstituted BCP Bpin **16**. Starting from secondary alkyl Bpins, a variety of C1, C2 and C3 trisubstituted BCPs, including C2-alkyl (**17**–**22**, **14**) and C2-aryl substituted (**23**) BCP Bpins were prepared. Lastly, subjecting tertiary alkyl Bpin starting materials to cyclization condensations afforded BCPs with di-substituted C2 side chains (**24**, **25**). The structures of BCPs **16**, **20** and **26** were unambiguously assigned by single crystal X-ray analysis. From this structural data, it is clear to observe that the substitution on the C2 of BCP reduces the C1–C2–C3 angle due to Thorpe–Ingold effect (75.7° in **16**, 73.6° in **20**, 72.1° in **26**). In addition to Ph at C1, other medicinal chemistry relevant motifs such as, halogenated aryls (4-chlorophenyl, **31**), electron-rich heterocycles (2-thiophene, **27**), and Lewis-basic heterocycles (3-pyridyl, **28**) were all compatible in this cyclization. Smaller alkyl substitutions, including methyl (A value = 1.7, **29**) or isopropyl (**30**) could also be incorporated at R1 to promote smooth cyclization to the corresponding products. It is noteworthy that the cyclization could also be performed with a variety of functional groups that allow for further downstream functionalizations, including amide (**32**), isopropyl ester (A value = 1.2, **33**), vinyl (A value = 1.35, **35**), terminal alkyne (A value = 0.41, **36**) and amine (**34**). In addition to the aryl- and alkyl substitutions at C2, productive cyclization of gem-diborylated[45] precursors provides the **37** di-Bpin substituted BCP. This substrate opens avenues for further diversification. The asymmetric BCP **38** was cyclized from its chiral Bpin precursor in a 69% yield with slightly ee erosion. Besides the above-mentioned substitutions on the cyclobutanone side chain (R^2 and/or R^3) to C2-substitued BCPs, the cyclobutane ring itself can be prefunctionalized

(Figure 3B). To that end, the methyl substituted cyclobutanone **39** (single diastereomer, stereochemistry unassigned) was cyclized to **17** in 42% yield. This compound exemplifies the possibility of accessing more complicated BCPs via cyclobutanone prefunctionalization.

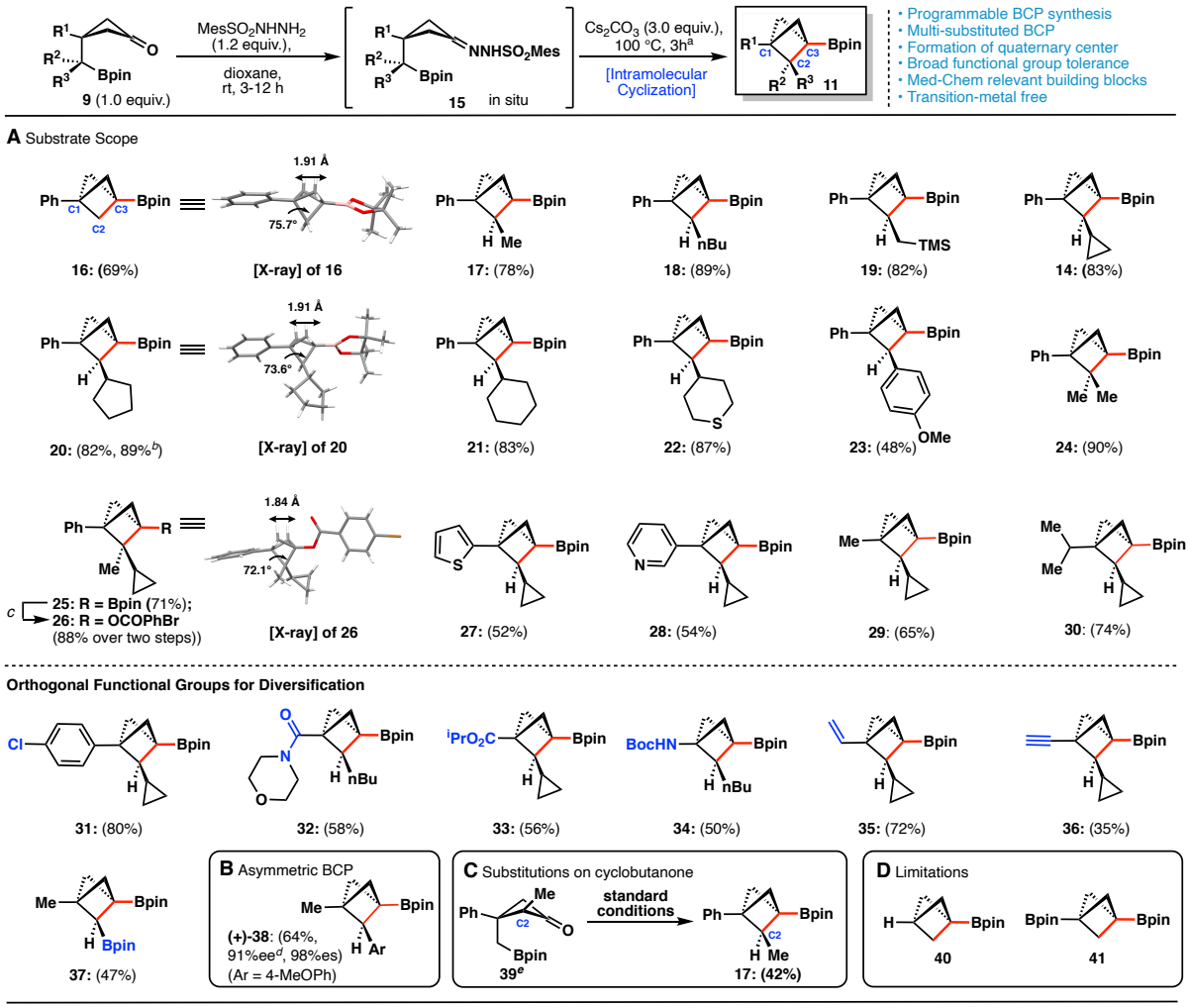


Figure 3. Substrate Scope of BCPs *via* Intramolecular Cyclization. Starting materials and products are racemic mixtures, unless annotated. (**A**) Substrate scope; (**B**) Asymmetric BCP example; (**C**) Substitutions on cyclobutanones; (**D**) Limitations of current reaction. Reaction conditions: [a] Cyclobutanone **9** (1.0 equiv.), $MesSO_2NHNH_2$ (1.2 equiv.) in dioxane (0.1-0.2 M) stirred at rt for 3-12 h, monitored by TLC; then Cs_2CO_3 (3.0 equiv.) was added and stirred at 100 °C for another 3 h; [b] 3.7 mmol scale;[c] 1) NaOAc, H_2O_2, 0 °C, 1 h; 2) DMAP, 4-bromobenzoyl chloride, DIPEA; [d] ee values were measured after conversion to their alcohol derivatives. [e] the stereochemistry is unassigned; See the Supplementary information for experimental details.

The robustness of this reaction was highlighted by accessing **20** on gram scale (3.7 mmol, 89%) in a similar yield to that on 0.1 mmol scale and under identical conditions. Consistent with our initial hypothesis that an axial conformation of the Bpin-containing side chain is crucial for the success of this cyclization, lower yields were observed when a smaller R^1 group was incorporated on the cyclobutanone starting material (as observed by A value trends, *vide supra*). Currently, the only limitation for this methodology (Figure 3C) was found when attempting the cyclization of substrates with a small R^1 group (e.g. R^1=H, **40**) and when R^1 = Bpin (**41**)[46].

As illustrated in Figure 4, the strategic impact of this methodology shines in its ability to combine the modularity of preparing C2-substituted BCP Bpins (*via* cross-coupling) and leveraging the plethora of existing transformations for Bpin functionalization for downstream diversification of the BCP bridgehead position. (Figure 4). For example, the oxidation of

boronic ester **20** led to the alcohol (**42**) in high yield. Additionally, **20** was subjected to Zweifel olefination[47,48], Aggwaral's arylation protocol[49], and Matteson homologation[50] to afford C–C bond-forming products **43**, **44** and **45**, respectively. The Bpin group can also be transformed to the more stable trifluoroborate salt (**46**), which opens further functionalization opportunities. Radical proto-deborylation[51] results in C1, C2-disubstitued BCPs (**47**), and C(sp^3)–C(sp^2) Pd catalyzed Suzuki cross-coupling conditions[52,53] enables arylation at the bridge head (**48**). Lastly, cross-coupling of the *in situ*-generated boronic acid with sulfonylhydrazone **49** affords the Bpin **50** in 92% yield. Therefore, this strategy allows for systematic introduction of substitutions at any position of the BCP, including the bridgeheads (C1 and/or C3) as well as the backbone (C2, mono- and di-). Importantly, this enables the practitioner to access a wide range of substituted BCPs that can serve as bioisosteres for ortho-, meta- or para-substituted benzene rings.

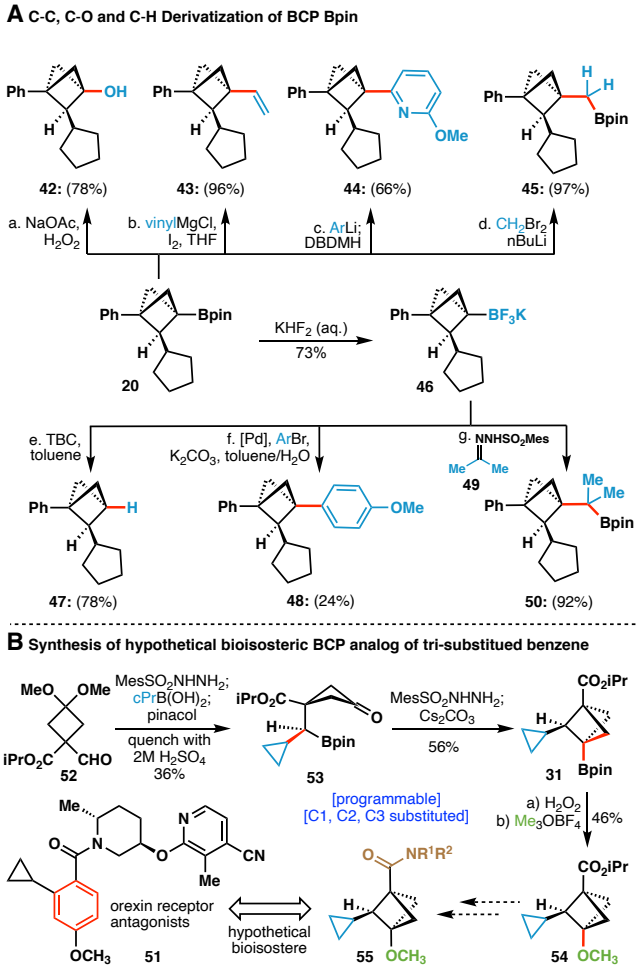


Figure 4. Derivatization and Synthetic Application of BCP Bpins. See the Supplementary information for experimental details.

As illustrated in Figure 4B, compound **51** was developed by Merck and Co. as an orexin receptor antagonists to treat insomnia[54]. While this drug possesses a 1,3,4-trisubstituted benzene ring within its structure, previous methods to access functionalized BCPs were not conducive to the preparation of a saturated trisubstituted analogue. In contrast, this methodology provides straightforward and modular access to its higher fraction sp^3 (Fsp^3) BCP analog **55**, via a sequence of 1) cPr installation (**53**), 2) cyclization (**31**), 3) Bpin oxidation to alcohol, 4) alkylation (**54**), and subsequent hydrolysis/amide coupling (**55**).

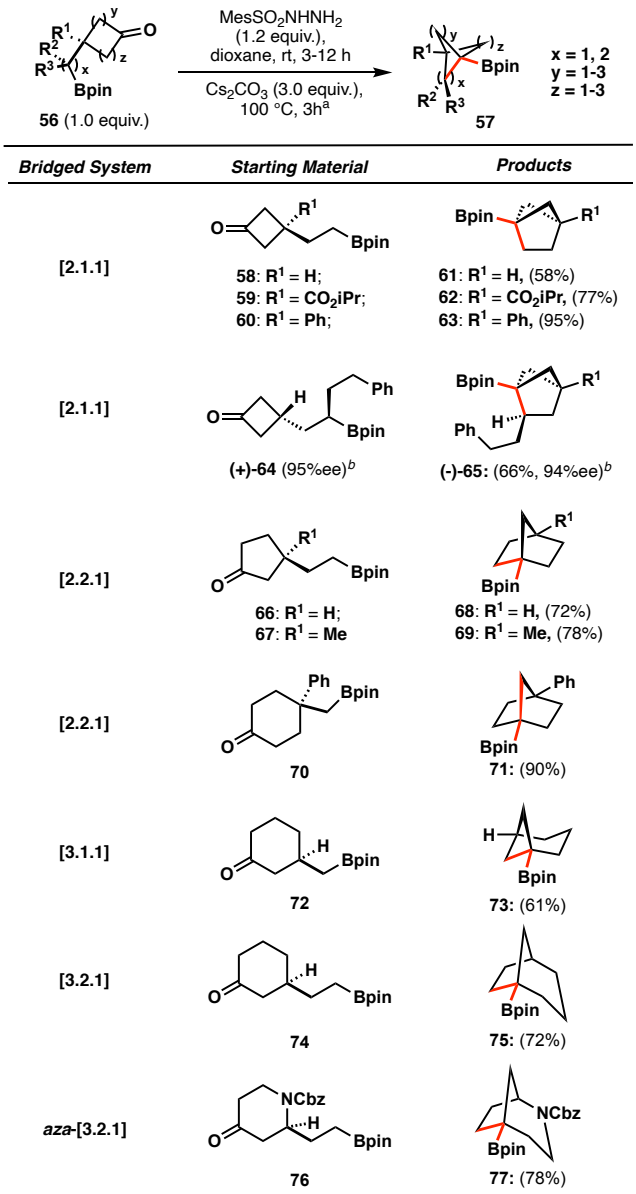


Figure 5. Intramolecular Cyclization to Access Other Bridged Systems. Starting materials and products are racemic mixtures, unless annotated. [a] Reaction conditions: Cyclic ketone **56** (1.0 equiv.), $MesSO_2NHNH_2$ (1.2 equiv.) in dioxane (0.1–0.2 M) stirred at rt for 3-12 h, monitored by TLC; then Cs_2CO_3 (3.0 equiv.) was added and stirred at 100 °C for another 3 h. [b] ee values were measured after conversion to alcohol derivatives. See the Supplementary information for starting material preparation and experimental details.

Besides BCPs, other bicyclic scaffolds have also been showcased or proposed as potential saturated bioisosteres. Often the bottleneck in performing SAR (Structure-Activity Relationship) studies on these ring systems, at the bridgehead positions in particular, is the lack of unified synthetic strategies to access suitable diversifiable building blocks. As delineated in Figure 5, this cyclization enables the construction of a wide range of bicyclic rings systems with the versatile Bpin preserved at the bridgehead position. Starting from a range of cyclobutanones (**58**–**60**, **64**), cyclopentanones (**66**, **67**) and cyclohexanones (**70**, **72**, **74**), in combination with pendant boronic ester side chains of varying length, bicyclo[2.1.1] (**61**–**63**, **65**), [2.2.1] (**68**, **69**, **71**), [3.1.1] (**73**) and [3.2.1] (**75**) systems were successfully prepared using these coupling conditions. Depending on the ease of accessibility of the starting material, [2.2.1] bicycles could be accessed from either cyclopentanones (**66**, **67**) or cyclohexanones (**70**). Saturated ring systems with a heteroatom embedded in them could also be prepared using this protocol, as demonstrated by the *aza*-[3.2.1]bicycle (**77**). Notably, starting from a chiral alkyl Bpin, this protocol allows for complete transfer of chiral

information into the bicyclic products and enables the asymmetric synthesis of these valuable bioisosteres. For example, the chiral cyclobutanone Bpin **64**[35] provided chiral [2.1.1] bicycle **65** with no erosion of ee.

In conclusion, we have developed a novel intramolecular cyclization to access C1-, C2-, and C3- substituted BCPs. As showcased in Figures 3–4, this operationally simple and chemoselective method enables rapid and modular preparation of a variety of synthetically challenging boronate-substituted BCPs. Synergistic application with existing Bpin functionalization strategies allows for rapid diversification and synthesis of complex bioisosteres that are highly desired in drug discovery. In addition, this method was successfully implemented to prepare a range of other pharmaceutically relevant bicyclic bioisosteres (Figure 5) that have yet to be fully explored. As a result, we expect this method to have a substantial impact within drug discovery, specifically in how benzene replacements are designed and incorporated into targets of interest.

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