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An intramolecular coupling approach to alkyl bioisosteres for the synthesis of multi-substituted bicycloalkyl boronates

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Abstract

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 an approach to accessing multi-substituted BCPs via a type of intramolecular cyclization. In addition to the C1, C3-disubstituted BCPs, this method also enables the construction of yet under-explored multi-substituted (C1, C2 and C3) BCPs from readily accessible cyclobutanones. The broad generality of this method is also examined through the 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 generated during the cyclization reaction is demonstrated via several downstream functionalizations, highlighting the ability of this approach to enable the programmed and divergent synthesis of multi-substituted bicyclic hydrocarbons.

Graphical Abstract

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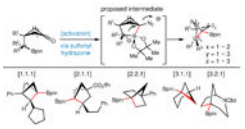
Author contributions

Y.Y., J.T. and T.Q. performed experiments; J.M.E.H., B.K.P., R.R.M., and T.Q. designed and supervised the project; J.M.E.H. and B.K.P. performed DSC experiments; Y.Y., J.T., J.M.E.H., R.R.M., and T.Q. wrote the paper.

Competing Interests

A provisional patent application naming T.Q., Y.Y., and J.T. as inventors has been filed by the Board of Regents of the University of Texas System, which covers the synthetic method and structural motifs described in this manuscript. The remaining authors declare no competing interests.



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[1–3]. Recent developments in medicinal chemistry shine a new light on the potential utility of these C(sp^3)-rich hydrocarbons[4]. Owing to their unique physical and chemical properties, bicyclic hydrocarbons exhibit the ability to modulate the pharmacokinetic and physiochemical properties of drug candidates (Figure 1a)[5–10]. Bicyclo[1.1.1]pentanes (BCPs) containing substitutions at bridgehead positions (C1, C3) are now widely recognized as saturated bioisosteres for para-substituted benzenes[11,12]. Analogously, related caged scaffolds with differentiated substitutions (Figure 1b) are expected to be ideal bioisosteres of ortho- or meta- substituted benzenes[13,14]. 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)[15–18], using methodologies pioneered by Wiberg[15,19], Michl[20], Baran[21,22], and others[23–41], wherein **6** is transformed to symmetric and asymmetric BCPs using either single- or two-electron transfer pathways (Figure 1c). These efforts have primarily focused on accessing C1 and/or C3- substituted BCPs until few recent reports[42–46] disclosed strategies for the systematic functionalization of the backbone (C2) of BCPs. In addition to the strain-release strategy, Wurtz coupling[47], Norrish–Yang cyclization[48], [2+2] photo-cycloaddition[49], ring expansion[44–46,50], and ring contraction[51] 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 an approach for the construction of multi-substituted BCPs via the intramolecular coupling of cyclobutane-tethered sulfonyl hydrazones and boronic esters (Figure 1d). 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.

Results and Discussion

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)[52]. However, previous studies indicated that base-initiated intramolecular substitution proved unsuccessful in BCP formation[53], presumably due to the unusual strain energy present in the desired target. Taking inspiration from our[54] and other's prior studies[55–63] 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**.[64,65] Alkyl boron pinacol esters (Bpin) have a priori been reported as recalcitrant coupling partners in Barluenga-Valdés coupling[55] and its modifications.[54] However, from both a practicality and ease of access perspective, alkyl Bpins were identified as ideal starting materials. We envisioned that an intramolecular reaction environment would facilitate the coordination by decreasing the entropic barrier, which might help overcome the poor coordinate reactivity of the Bpin, thereby enabling the intramolecular reaction to occur.

Reaction optimization.

To test this theory, the key intermediate **13** was prepared in one-step using our boron-preserving cross-coupling conditions from cyclobutane aldehyde **12** (Table 1)[54]. 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 Table 1; see Page 34 in Supplementary Information for detailed reaction optimizations) 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).

Reaction scope for BCPs.

With the optimal conditions in hand, the substrate scope of this intramolecular cyclization to access di-, tri-, and tetra-substituted BCPs was systematically investigated (Table 2). 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[66,67]. A-values are the conformational preference of an equatorial compared to an axial substituent in a monosubstituted cyclohexane. The cyclobutanone Bpins **9** were prepared from the corresponding aldehydes, ketones, esters and halides[68–73]. A primary alkyl Bpin (R^2 = H, R^3 = H) underwent smooth cyclization to the C1, C3 di-substituted BCP Bpin **16**. Starting from secondary alkyl Bpins, a variety of C1, C2 and C3 tri-substituted 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 that increased C2-substitution reduces the C1–C2–C3 angle, presumably due to the 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 (A value = 2.15, **30**) could also be incorporated at R^1 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[59,70] precursors provide the di-Bpin substituted BCPs (**37** and **38**). These substrates open avenues for further diversification. The asymmetric BCP **39** was cyclized from its enantioenriched Bpin precursor in a 69% yield with a high level of chiral fidelity. Besides the above-mentioned substitutions on the cyclobutanone side chain (R^2 and/or R^3), the cyclobutane ring itself can be prefunctionalized. To that end, the methyl substituted cyclobutanone **40** was cyclized to **17** in 42% yield. This example highlights the possibility of accessing more complicated BCPs via cyclobutanone prefunctionalization.

The robustness of this reaction was highlighted by accessing **14** and **20** on gram scale (4.8 mmol and 18 mmol) in a similar yield (75% and 79%) to that on 0.1 mmol scale and under identical conditions. In addition, gram-scale cyclization of gem-diborylated precursors afforded 2.0 g and 6.6 g of di-Bpin substituted BCPs **37** and **38** in 53% and 50% yield, respectively. Consistent with our initial hypothesis that an axial conformation of the Bpin-containing side chain is crucial for the success of this cyclization, small substituents were tolerated (R^1 = Me, vinyl and ethynyl) but no reactivity was observed when R^1 = H and Bpin (**41** and **42**[74]).

Synthetic applications.

As illustrated in Figure 2a, 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. For example, the oxidation of boronic ester **20** led to the alcohol (**43**) in high yield. Additionally, **20** was subjected to Aggarwal's arylation protocol[75], Zweifel olefination[76,77], and Matteson

homologation[78] to afford C–C bond-forming products **44**, **45** and **46**, respectively. The Bpin group can also be transformed to the more stable trifluoroborate salt (**47**), which opens further functionalization opportunities. Radical proto-deborylation[79,80] results in C1, C2-disubstitued BCPs (**48**), and C(sp^3)–C(sp^2) Pd catalyzed Suzuki cross-coupling conditions[81–83] enables arylation at the bridgehead (**49–51**) (See page 36–37 in Supplementary Information for detailed optimization). Furthermore, cross-coupling of the in-situ-generated boronic acid with sulfonylhydrazone **52** affords the Bpin **53** in 92% yield. Amination with alkyl azides through BF_3•Et_2O activation of affords amines **54–56** in moderate yields (See page 38–39 in Supplementary Information for detailed optimization).[84,85] 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.

As illustrated in Figure 2b, compound **57** was developed as an orexin receptor antagonist to treat insomnia[86]. 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 tri-substituted BCP analogue. In contrast, this methodology provides straightforward and modular access to the intermediate **60** for its higher fraction sp^3 (Fsp^3) BCP analog **61**, via a sequence of 1) cPr installation (**59**), 2) cyclization (**33**), 3) Bpin oxidation to alcohol, and 4) alkylation (**60**).

Reaction scope for other bicyclic scaffolds.

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 Table 3, this cyclization strategy enables the construction of a wide range of bicyclic ring systems with the versatile Bpin preserved at the bridgehead position. Starting from a range of cyclobutanones (**64**–**66**, **70**), cyclopentanones (**72**, **73**) and cyclohexanones (**76**, **78**, **80**), in combination with pendant boronic ester side chains of varying length, bicyclo[2.1.1] (**67**–**69**, **71**), [2.2.1] (**74**, **75**, **77**), [3.1.1] (**79**) and [3.2.1] (**81**) 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 (**72**, **73**) or cyclohexanones (**76**). 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 (**83**). Notably, starting from a chiral alkyl Bpin, this protocol allows for complete transfer of stereochemistry into the bicyclic products and enables the asymmetric synthesis of these valuable bioisosteres. For example, the chiral cyclobutanone Bpin **70**[69] provided chiral [2.1.1] bicycle **71** with no erosion of enantiomeric excess (e.e.).

In conclusion, we have developed an intramolecular cyclization to access C1-, C2-, and C3- substituted BCPs. As showcased in Table 2 and Figure 2, 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 (Table 3) 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.

Methods

Caution:

In the reactions to prepare BCP precursors and the cyclization reactions to afford BCP derivatives, an equivalent of nitrogen is released. In the multi-gram scale procedure, hydrogen and nitrogen are released and the reaction is exothermic. Please handle carefully when conducting the reported reactions in a large scale.

General procedure for synthesis of bicycloalkyl boronates.

A screw-capped culture tube was charged with ketone (1.0 equiv.), 2-mesitylenesulfonyl hydrazide (1.2 equiv.) and dried dioxane (0.1 M). The mixture was then stirred at room temperature until the completion of the reaction showed by TLC analysis (usually 3 – 12 h). Cesium carbonate (3.0 equiv.) was added, and the headspace of the tube was purged with a gentle stream of argon for approximately 10 seconds. The system was stirred at 100 °C under argon atmosphere for 3 hours. The suspended solution was then filtered over Celite and washed with diethyl ether. The solvent was removed under high vacuum, and the crude residue was purified by chromatography on silica gel.

Data Availability

Experimental data as well as characterization data for all compounds prepared in the course of these studies are provided in the Supplementary Information of this manuscript. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2062923 (**16**), 2062924 (**20**), 2062925 (**26**) and 2081087 (**40-ester**, see X-ray Crystallographic Data in Supplementary Information). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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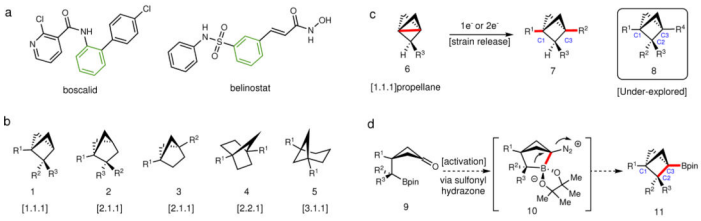


Fig. 1. Bridged hydrocarbons and BCPs syntheses.

(**a**) Representative drugs bearing ortho- or meta-substituted benzene ring: boscalid and belinostat. (**b**) Substituted hydrocarbons providing novel chemical space as potential bioisosteres. (**c**) The state-of-art for BCP synthesis (> 200 reports) from propellane **6** by using strain releasing strategy (left); under-explored C2-substituted BCPs and chiral BCPs (right). (**d**) Proposed intramolecular cyclization to access strained multi-substituted BCPs from cyclobutanone.

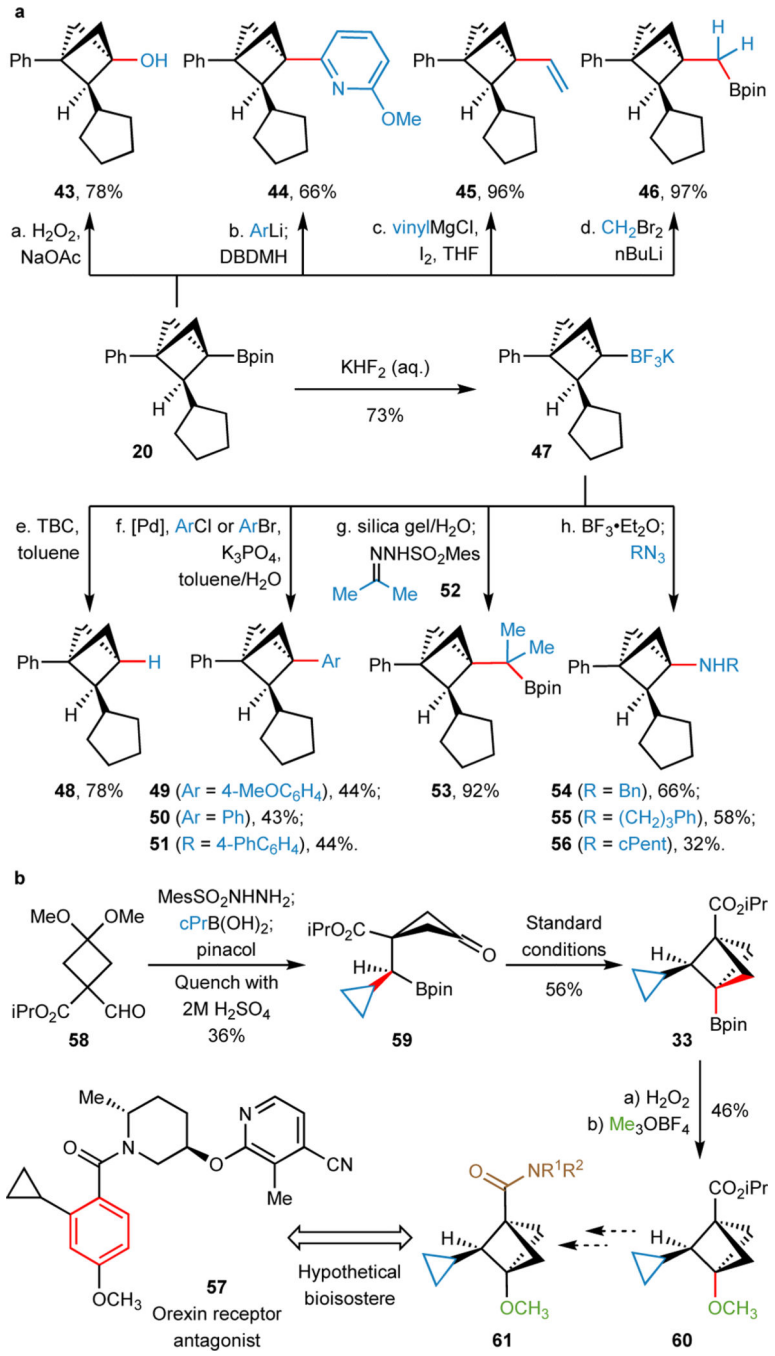


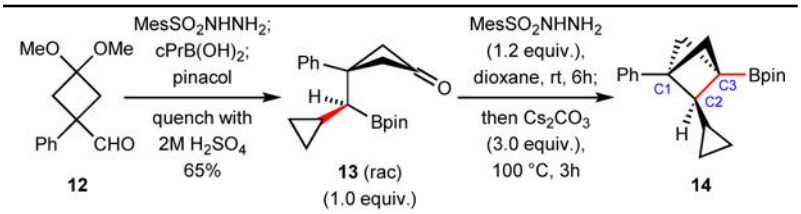
Fig. 2. Derivatization and Synthetic Application of BCP Boronates.

(**a**) Transformations of functional boronates for downstream diversification of the BCP bridgehead position, including oxidation (**43**), arylation (**44**), Zweifel olefination (**45**), Matteson homologation (**46**), radical proto-deborylation (**48**), Suzuki cross-coupling (**49**–**51**), hydrazone coupling (**53**) and amination (**54**–**56**); (**b**) Programmable synthesis of C1, C2, C3-trisubstituted BCP **60**, a versatile building block amenable for the preparation of hypothetical bioisosteres of an orexin receptor antagonist **57**. See “Additional Optimization of Suzuki Cross-Couplings and Aminations with 2-Substituted BCP Boronates” and

"Experimental Procedures and Characterization Data of Substrates (compound 43–60)" in Supplementary Information for details.

Table 1.

Intramolecular coupling optimization to access C2-substituted BCPs.



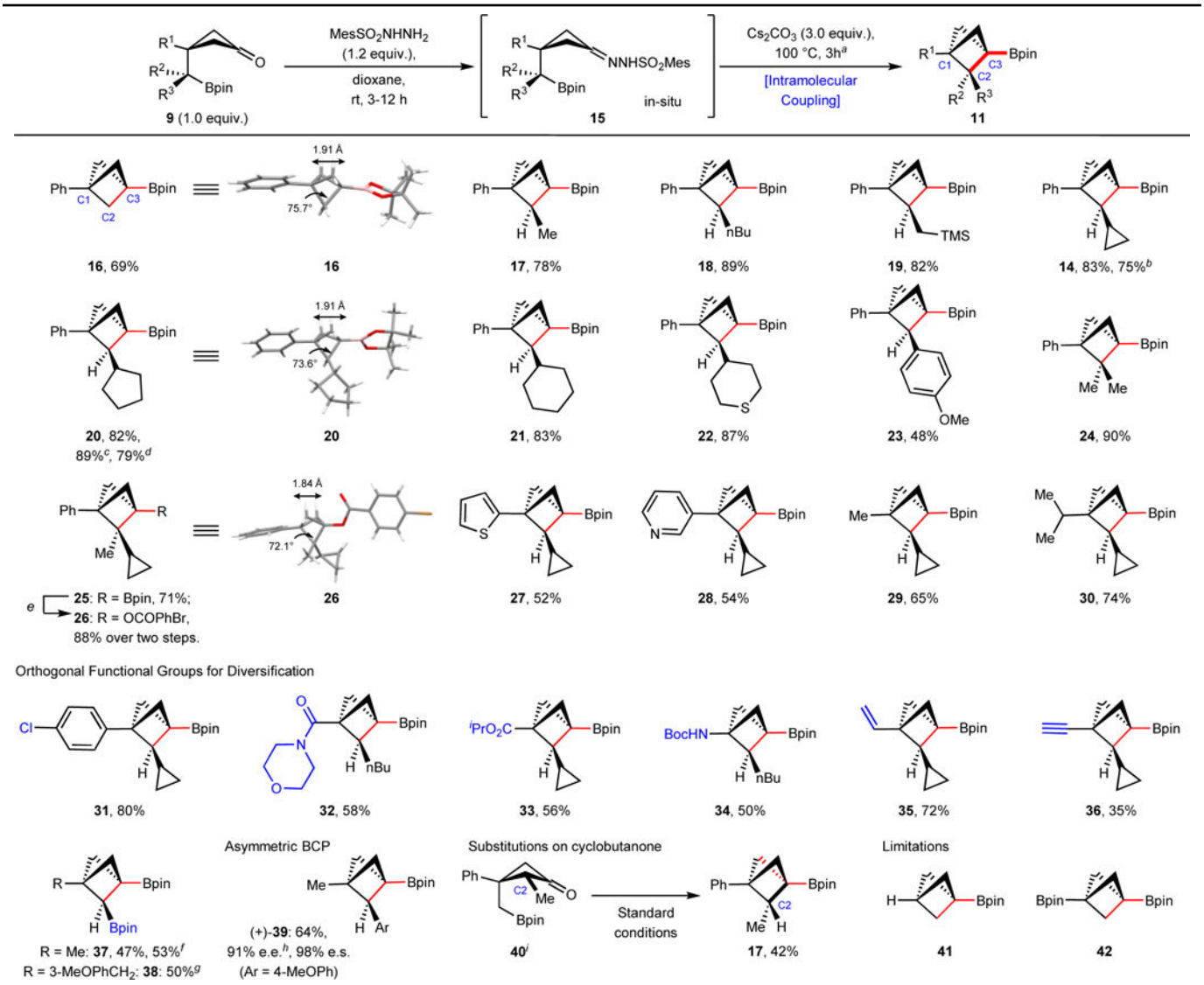
Entry	Deviation from above (**13** to **14**)	Yield (%)[a,b]
1	None	88 (83)
2	$TsNHNH_2$ in place of $MesSO_2NHNH_2$	63
3	$TrisylNHNH_2$ in place of $MesSO_2NHNH_2$	67
4	K_2CO_3 in place of Cs_2CO_3	26
5	KO*t*Bu in place of Cs_2CO_3	18
6	PhCl in place of dioxane	78
7	DMF in place of dioxane	52
8	Reaction 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 the isolated yield. rt, room temperature; Mes, mesityl; cPr, cyclopropyl; Ts, tosyl; Trisyl, triisopropylbenzenesulfonyl; DMF, N,N-dimethylformamide.

Table 2.

Substrate scope of BCPs via intramolecular coupling.



Starting materials and products are racemic mixtures, unless annotated.

[a] Reaction condition: Cyclobutanone **9** (1.0 equiv., 0.05–1.0 mmol), $MesSO_2NHNH_2$ (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] 4.8 mmol scale;

[c] 3.7 mmol scale;

[d] 18 mmol scale;

[e] Reaction condition: 1) NaOAc, H_2O_2, 0 °C, 1 h; 2) DMAP, 4-bromobenzoyl chloride, DIPEA;

[f] 11 mmol scale;

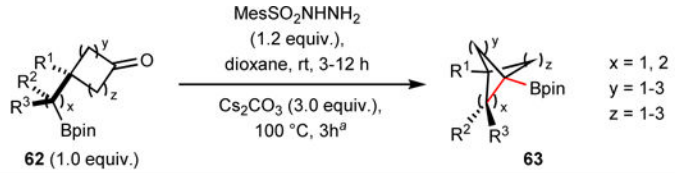
[g] 30 mmol scale;

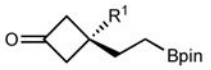
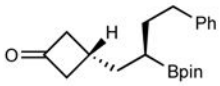
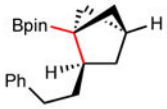
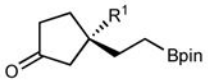
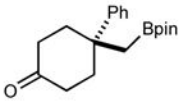
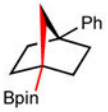
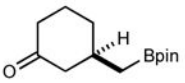
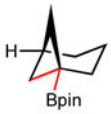
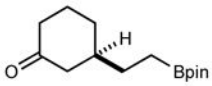
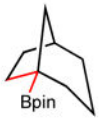
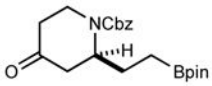
[h] e.e. values were measured after conversion to their alcohol derivatives;

[i] the stereochemistry was assigned based on its derivative; TMS, trimethylsilyl; Boc, tert-butyloxycarbonyl; DMAP, 4-dimethylaminopyridine; DIPEA, N,N-diisopropylethylamine; e.e., enantiomeric excess; e.s., enantiospecificity.

Table 3.

Intramolecular coupling to access bridged systems.



Bridged system	Starting material	Products
[2.1.1]	 **64** (R^1 = H); **65** (R^1 = CO_2iPr); **66** (R^1 = Ph).	 **67** (R^1 = H), 58%; **68** (R^1 = CO_2iPr), 77%; **69** (R^1 = Ph), 95%.
[2.1.1]	 (+)-**70,** 95% e.e.[b]	 (–)-**71**, 66%, 94%ee[b]
[2.2.1]	 **72** (R^1 = H); **73** (R^1 = Me).	 **74** (R^1 = H), 72%; **75** (R^1 = Me), 78%.
[2.2.1]	 **76**	 **77**, 90%
[3.1.1]	 **78**	 **79**, 61%
[3.2.1]	 **80**	 **81**, 72%
aza-[3.2.1]	 **82**	 **83**, 78%

Starting materials and products are racemic mixtures, unless annotated.

[a] Reaction conditions: Cyclic ketone **62** (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] e.e. values were measured after conversion to alcohol derivatives. Cbz, benzyloxycarbonyl.