Dibromocarbene Addition to Bicyclo[1.1.0]butanes: A Facile Route to Substituted Bicyclo[1.1.1]pentanes

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ABSTRACT: Strained, multicyclic hydrocarbons are increasingly important structural motifs for drug discovery. In particular, substituted bicyclo[1.1.1]pentanes (BCPs) have risen to prominence as bioisosteres for the ubiquitous benzene ring. Despite their favorable pharmacokinetic properties, synthetic strategies towards BCPs suffer from significant drawbacks – namely an overreliance on [1.1.1]propellane – an operationally challenging to utilize starting material which complicates scale-up and hampers widespread adoption of these motifs. In this work, the synthesis of 2,2-dibromo BCPs is described, presenting a class of novel substituted BCPs and circumventing the need for [1.1.1]propellane-based precursors. Scalable access to these compounds is demonstrated in a simple and inexpensive process, and their applicability for medicinal chemistry campaigns is highlighted through the synthesis of a diverse range of valuable building blocks – including highly sought-after bridge arylated BCP derivatives which are prepared *via* a novel electrocatalytic cross-coupling procedure.

INTRODUCTION

Substituted benzene rings are ubiquitous architectures present in biologically active molecules.[1] However, recent trends in medicinal chemistry have highlighted the need to "*Escape from Flatland,*"[2, 3] by substituting planar aromatic rings with alternative scaffolds bearing higher degrees of saturation and accordingly, greater three-dimensionality.[4, 5] Bicyclo[1.1.1]pentanes (BCPs) have risen to prominence as suitable bioisosteres (Figure 1A), often demonstrating improved solubility, metabolic stability and binding specificity over their benzene analogues.[6-10] Indeed, drug candidates containing BCP frameworks developed by Gilead and Denali Therapeutics have recently entered into clinical trials (Figure 1B),[11, 12] highlighting the relevance of the motif within medicinal chemistry campaigns.

The most heavily utilized strategies to access BCP fragments[13] originate with the highly strained hydrocarbon [1.1.1]propellane.[14] Ring-opening of [1.1.1]propellane *via* radical or polar pathways can afford valuable bridgehead substituted BCPs.[15-18] Despite the myriad ways in which this can be accomplished, such strategies suffer from the so-called "propellane problem."[13] Specifically, the use of [1.1.1]propellane is associated with several practical downsides, namely cost, use of harsh reaction conditions, relative instability of the parent hydrocarbon and operational difficulty associated with handling the volatile compound in solution.[13] These factors limit the practical utility of propellane-based methods and warrant investigation of distinct routes to BCP scaffolds,[19-21] with a particular focus on methodologies amenable to industrial scale applications, a prerequisite for the use of BCP in therapeutic development programs.

A lesser utilized route to access BCPs is *via* the addition of dihalocarbenes (**:CX_2**) to bicyclo[1.1.0]butanes (BCBs) (Figure 1C). In contrast with [1.1.1]propellane, BCBs offer pronounced benefits in their ease-of-handling, and can be readily accessed with a variety of substitution patterns and on large scales, making this synthetic route an attractive alternative.[22-24] Initially disclosed by Applequist in 1982,[25] the addition of dichlorocarbene (**:CCl_2**) to afford Cl_2-BCPs quickly found application in the synthesis of perdeuterated [1.1.1]propellane by Wiberg in 1985,[26] and more recently in the gram scale synthesis of a therapeutic lead by Hirst in 2016.[6] Access to bridge-fluorinated BCPs (from **:CF_2**) was first reported in 2019,[27, 28] and subsequent studies have communicated additional conditions for the generation of **:CF_2** and further derivatization of these building blocks.[29-34] Finally, we reported the addition of **:CBrF** to BCBs in 2022, which after reduction of the C–Br bond, afforded the first examples of bridge monofluorinated BCPs for use in medicinal chemistry campaigns.[35]

To date, there are no reports of successful addition of a heavier carbene homologue – e.g., dibromocarbene, **:CBr_2** –

to BCBs. Nevertheless, BCPs brominated at the bridge positions have garnered recent interest as viable synthetic precursors to 2-substituted BCP scaffolds, which are valuable for their potential as *ortho*- or *meta*-substituted benzene ring bioisosteres.[36, 37] Currently only a single route to access these brominated BCPs is known,[36] starting from synthetic precursors derived ultimately from [1.1.1]propellane. The aforementioned "propellane problem" therefore complicates the general applicability of this methodology, and as such, there is an urgent need for new approaches to substituted BCP scaffolds which circumvent the unwieldy use of [1.1.1]propellane.

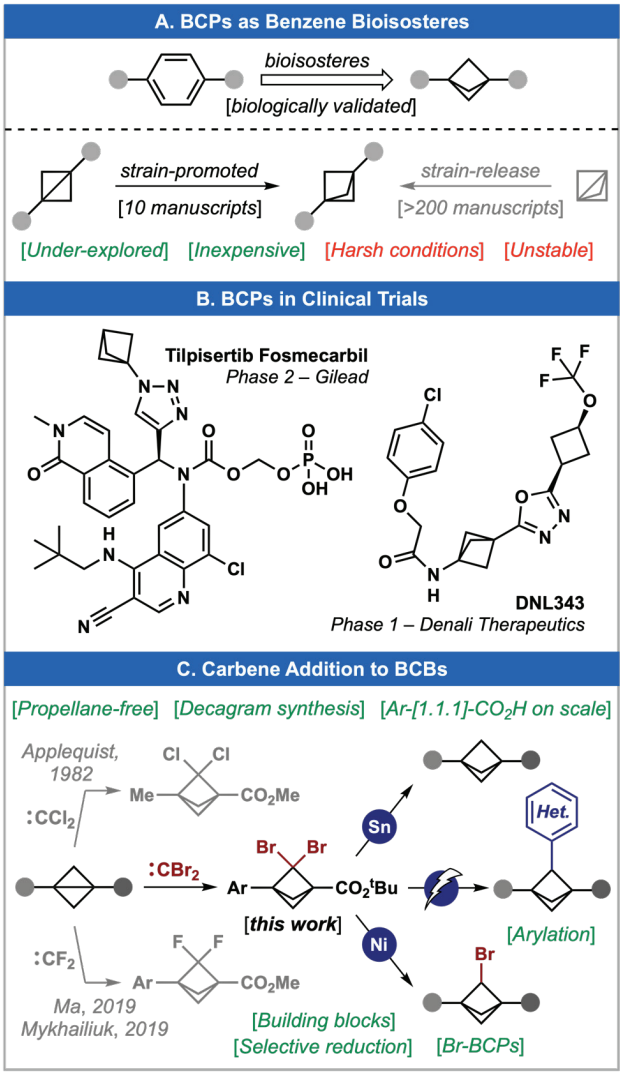


Figure 1. A: Bicyclo[1.1.1]pentanes (BCPs) as bioisosteres of benzene rings and their access from [1.1.1]propellane or bicyclo[1.1.0]butanes. B: Bioactive compounds in clinical trials containing BCPs. C: Carbene addition to BCBs affords substituted BCPs.

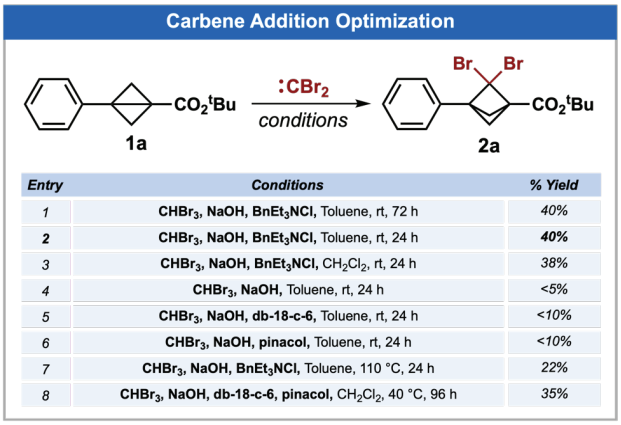
With these factors in mind, we sought to investigate the reactivity of **:CBr$_2$** towards BCBs to access a previously unexplored class of dihalogenated BCPs. Herein, we report the synthesis of a suite of structurally diverse Br$_2$-BCPs and demonstrate the versatility of these compounds through the scalable, selective reduction of the *gem*-dibromide unit to afford either the monobromide, or doubly-dehalogenated BCPs – compounds of direct interest to both medicinal and process chemists – as well as precursors to a broad suite of structurally diverse BCPs. Furthermore, motivated by the recent demonstration of cross-electrophile coupling (XEC) utilizing the monobromide BCP scaffold,[36] we report a novel nickel electrocatalytic C(sp^3)–C(sp^2) cross-coupling for the reductive arylation of Br$_2$-BCPs – providing direct access to valuable C2-modified BCPs.

RESULTS AND DISCUSSION

Development of Dibromocarbene Addition to BCBs: We commenced our investigations with model BCB **1a**, bearing an aryl group and an ester at the bridgehead positions (Table 1).[35] With a suitable precursor in hand, we first attempted to translate our previously reported conditions for the reaction of BCBs with bromofluorocarbene – generated by deprotonation of dibromo(fluoro)methane in toluene with concentrated NaOH in the presence of a phase-transfer catalyst ($BnEt_3NCl$).[35]

In this instance, substituting the freon for bromoform to generate **:CBr$_2$** *in situ* pleasingly afforded the desired product **2a** in an acceptable yield of 40% (entry 1). Subsequent screening of alternative conditions identified that the reaction time could be shortened to 24 h without a decrease in yield (entry 2), and that DCM was a comparable solvent to toluene (entry 3). Only trace product was formed without a phase transfer catalyst (entry 4), and alternative phase transfer catalysts were suboptimal (entries 5 and 6). An increase in reaction temperature was detrimental to the yield (entry 7) and alternative combinations of phase transfer catalysts, solvent and temperature also failed to improve the outcome (entry 8).[38]

Table 1. Optimization of dibromocarbene (:CBr$_2$) addition to bicyclo[1.1.0]butanes.



Entry	Conditions	% Yield
1	$CHBr_3$, NaOH, $BnEt_3NCl$, Toluene, rt, 72 h	40%
2	$CHBr_3$, NaOH, $BnEt_3NCl$, Toluene, rt, 24 h	**40%**
3	$CHBr_3$, NaOH, $BnEt_3NCl$, CH_2Cl_2, rt, 24 h	38%
4	$CHBr_3$, NaOH, Toluene, rt, 24 h	<5%
5	$CHBr_3$, NaOH, db-18-c-6, Toluene, rt, 24 h	<10%
6	$CHBr_3$, NaOH, pinacol, Toluene, rt, 24 h	<10%
7	$CHBr_3$, NaOH, $BnEt_3NCl$, Toluene, 110 °C, 24 h	22%
8	$CHBr_3$, NaOH, db-18-c-6, pinacol, CH_2Cl_2, 40 °C, 96 h	35%

With a validated protocol for the addition of **:CBr$_2$** to BCBs established, we proceeded to synthesize a suite of BCBs (**1b–o**, 30–53% yield over 4 steps) with varying aryl substituents at the BCB 3-position (Figure 2) to demonstrate the generality of the carbene addition reaction. Employing the optimal reaction conditions identified for the synthesis of **2a** (entry 2, Table 1), Br$_2$-BCPs bearing simple electron donating (Me: **2b–d,** ^{t}Bu: **2e** and OMe: **2f**; 32–41% yields) and withdrawing (F: **2g**, **2h** and CF$_3$: **2k**, **2l**; 29–32% yields) substituents were formed in similar efficiency to the parent compound **2a**. Aryl bromides **2i** and **2j** (34% and 30% yield) provide additional handles for further functionalization at a later stage,[32] and the CF$_3$ ethers (**2m**; 31% and **2n**; 33% yield) and CF$_3$-cyclopropyl (**2o**; 34% yield) derivatives are of medicinal chemistry interest.[39-41]

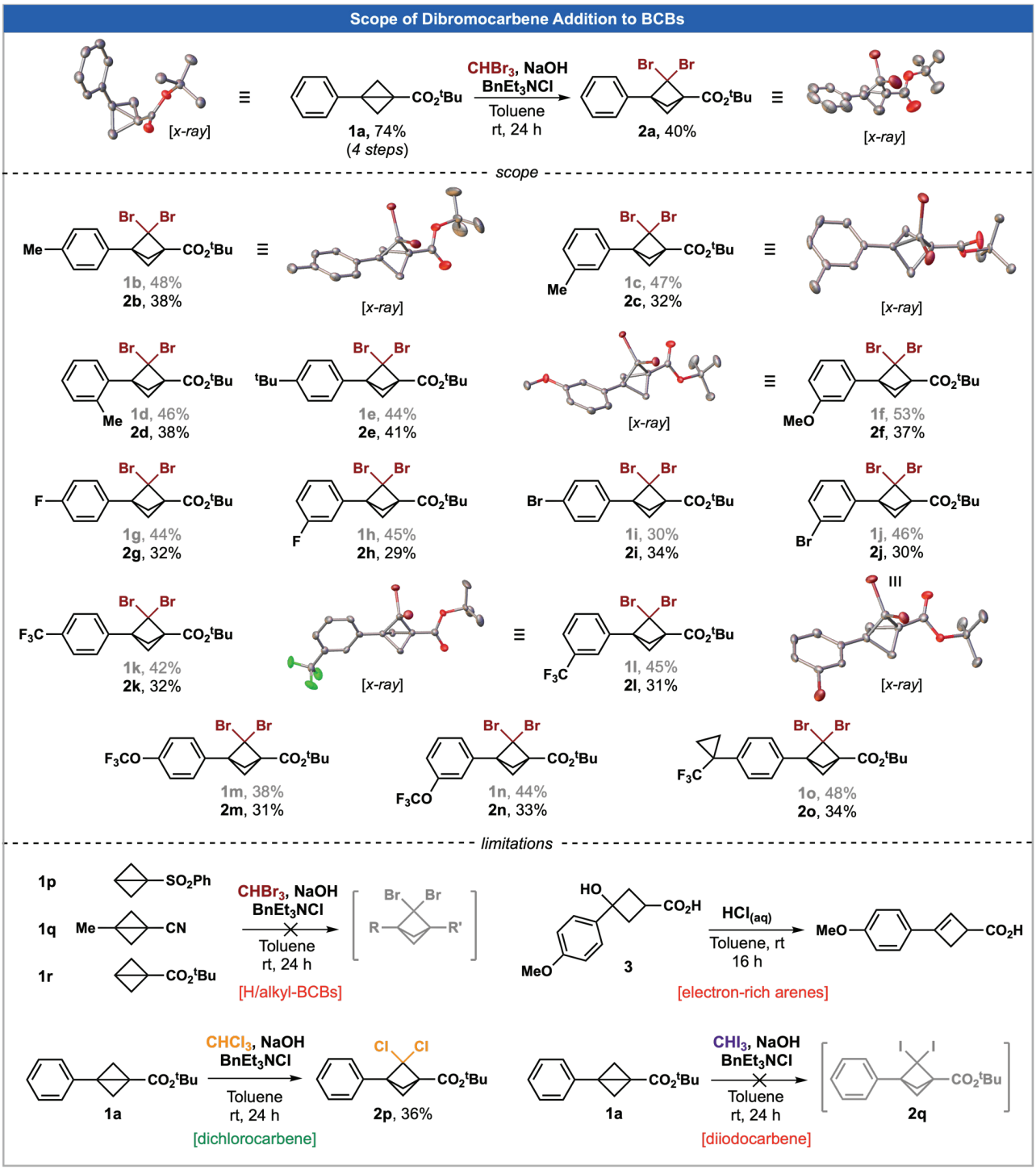


Figure 2. Scope and limitations of carbene addition to bicyclo[1.1.0]butanes (BCBs) to afford 2,2-dibromo-3-arylbicyclo[1.1.1]pentanes.

Several limitations to this reaction were identified: BCBs lacking an aryl substituent (**1p-r**) are not tolerated in the carbene addition reaction, and although the carbene precursor can be replaced with chloroform (to generate Cl_2-BCP **2p**), use of the heavier iodoform did not furnish desired I_2-BCP **2q**. Additional limitations were identified in the preparation of the BCB precursors, with electron rich arenes (**3**) incompatible with this synthetic route.

Next, we investigated the scalability of the carbene addition reaction (Figure 3). Precursor BCB **1a** can be easily prepared from cheap and readily available cyclobutane derivative **4** ($0.64 USD per gram) according to literature procedure,[35] a process that requires no chromatographic separation, greatly enhancing time and cost efficiency. Increasing the scale of the carbene addition reaction to 75 g resulted in a slightly diminished yield of **2a** (35%). Deprotection of the *tert*-butyl ester afforded the free acid building block **8**, with 38 g of bench-stable product isolated in a single run using this procedure.

Physicochemical Properties: With scope and limitations of the dibromocarbene addition reaction established, we next moved to study the physicochemical properties of Br_2-BCPs (Table 2).

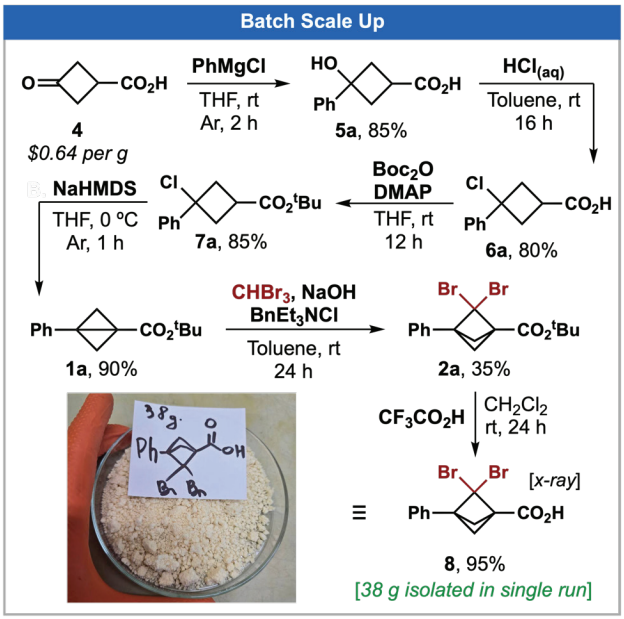


Figure 3. Batch scale up of 2,2-dibromobicyclo[1.1.1]pentane (BCP) synthesis to provide BCP carboxylic acid building block **8**.

First, we experimentally determined the acidity of carboxylic acids **8** (CBr_2) and **9** (CH_2). Incorporation of the *gem*-Br_2 moiety into the BCP core reduced the acidity of the carboxylic group by one pK_a unit: 5.1 (**9**, CH_2) *vs* 4.1 (**8**, CBr_2). Interestingly, this effect was similar to the *gem*-Cl_2 analogue **11** (pK_a 4.1) and weaker compared to the *gem*-F_2 analogue **10** (pK_a 3.9).

Next, we synthesized five model amides **12-16** and studied their solubility, lipophilicity, and metabolic stability. Incorporation of the *gem*-Br_2 moiety into the BCP scaffold reduced the water solubility: 266 µM (**13**) *vs* 151 µM (**16**); increased the lipophilicity, logD: 3.2 (**13**) *vs* 4.2 (**16**); and dramatically decreased the metabolic stability, CL_{int} (µL min^{-1} mg^{-1}) = 24 (**13**) *vs* 139 (**16**). These results make Br_2-BCP a non-desirable replacement of benzene/BCP rings in medicinal chemistry projects. In contrast, more soluble, stable and less lipophilic F_2-BCP is more promising for analogous replacements. Despite their metabolic liabilities, Br_2-BCPs present ideal starting materials for the preparation of functionalized bicyclo[1.1.1]pentanes *via* functionalization of the C–Br bond.

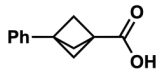
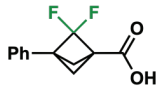
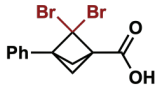
Building Block Synthesis and Dibromide Reductions: We next turned our attention to investigating the reactivity of Br_2-BCPs to synthesize a range of useful building blocks (Figure 4).

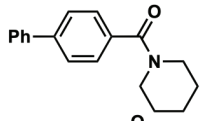
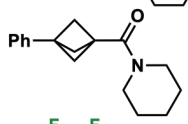
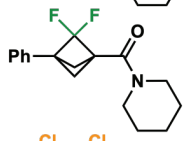
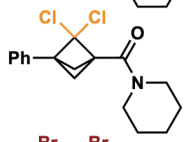
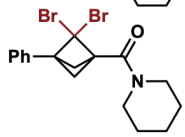
Bridgehead modifications of Br_2-BCP **8** were performed on decagram scale in good yields (Figure 4A). Esterification of the carboxylic acid afforded methyl ester **17**, and subsequent oxidative cleavage of the phenyl ring furnished monomethyl dicarboxylate BCP **18**, a valuable orthogonally protected building block for further derivatization.

Given the prevalence of halogen-free BCPs and the emergence of monobromo BCPs in the literature, we next sought to establish conditions to reduce the *gem*-dibromide functionality to access these highly sought after motifs.

Table 2. Experimental pKa Values of BCP Carboxylic Acids and Physicochemical Properties of Amides.

Physicochemical Properties of Br_2-BCPs

	Carboxylic acid	pK_a
9		5.10 ± 0.05
10		3.89 ± 0.05
11		4.14 ± 0.05
8		4.09 ± 0.05

	Model compound	*Sol.*	*logD*	CL_{int}	$t_{1/2}$
12		67	3.6	12	139
13		266	3.2	24	70
14		91	3.5	19	86
15		116	3.7	65	26
16		151	4.2	139	12

Solubility: the experimental kinetic solubility in phosphate-buffered saline, pH 7.4 (µM). *logD* (7.4): the experimental distribution coefficient in *n*-octanol/phosphate-buffered saline, pH 7.4. Reliable *logD* values could be obtained within a range of 1.0–4.0. CL_{int}: the experimental metabolic stability in human liver microsomes (µL min^{-1} mg^{-1}). $t_{1/2}$ (min): the experimental half-time of a metabolic decomposition.

Following literature precedent for the two-fold reduction of dichloro BCPs,[6, 25, 26] the reducing agent tributylstannane in combination with radical initiator AIBN was applied to Br_2-BCPs **2b**, **e**, **h**, **k** and **m** (Figure 4B). Gratifyingly, each compound was successfully reduced, and TFA treatment of the crude reaction mixture allowed for simple isolation of the free acids **19b**, **e**, **h**, **k** and **m**, in good yields (60–72%) across the two steps. Free acid BCPs **19h** and **m** were then subjected to modified Curtius rearrangement conditions to afford BCP amines **20h** and **m** in good yields (75% and 70%, respectively). Importantly, these transformations could be performed on decagram scale, offering convenient access to valuable BCP moieties.

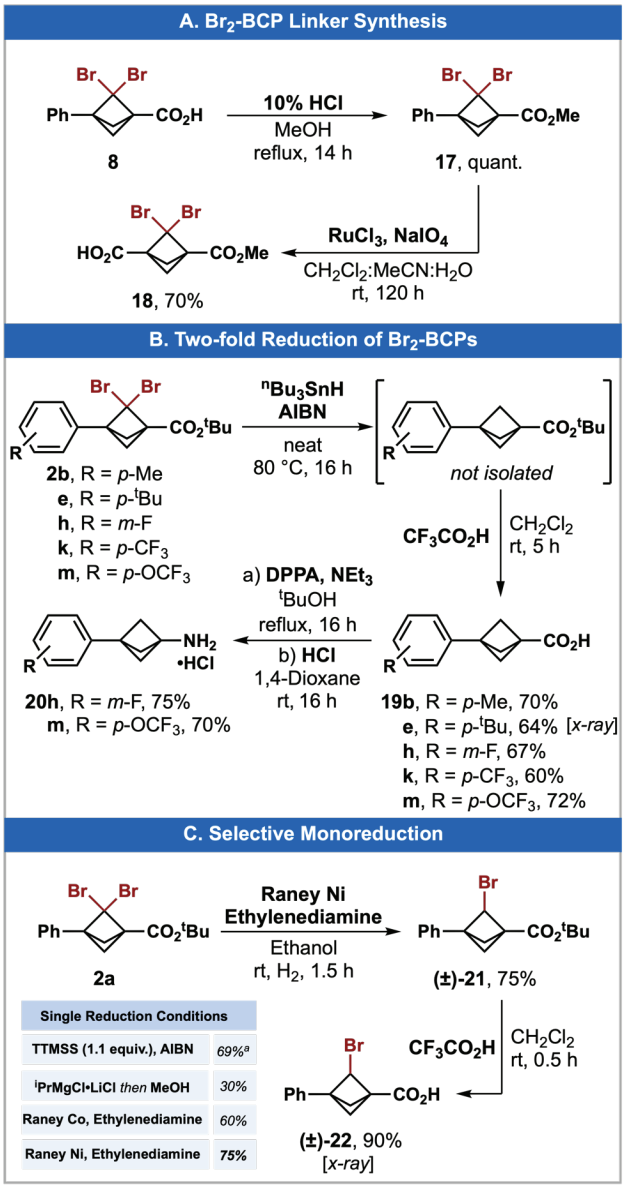


Figure 4. A: Synthesis of Br_2-BCP linker **18**. B: Two-fold dehalogenation of Br_2-BCPs to afford carboxylic acid and amine building blocks. C: Selective monoreduction of Br_2-BCP **2a** to Br-BCPs **(±)-21** and **(±)-22**. [a] % yield determined by qNMR with 1,3,5-trimethoxybenzene as internal standard.

With conditions established to fully reduce the dibromide to the corresponding BCP, we next focused on developing an approach to selective monoreduction to expand access to monobromo BCPs for late-stage modification (Figure 4C). Akin to tributylstannane, tris(trimethylsilyl)silane (TTMSS) has been shown to act as a competent reducing agent in combination with radical initiators such as AIBN.[42] We envisioned that careful control of stoichiometry, coupled with the relative ease of reduction of the first C–Br bond would allow for the selective formation of a monobromo BCP. Although this combination was effective, affording the desired BCP **(±)-21** in 69% yield (NMR yield), isolation of the desired compound was onerous, as trace amounts of starting material and fully debrominated BCP persisted as inseparable byproducts. We next attempted a metal-halogen exchange with Knochel's turbo-Grignard[43] followed by simple quenching with a Brønsted-Lowry acid. Although this route led to full consumption of starting material, the desired monobromide **(±)-21** was only afforded in 30% yield.

Continuing our search for suitable reducing conditions, our attention turned to Raney metals, which have been shown to mono-reduce dibromocyclopropanes, although selectivity is typically attributed to steric demands of the pendant substituents.[44] Indeed, Raney Ni was found to be a proficient catalyst for reduction of the BrF-BCP in our previous work.[35] In the present study, treatment of the Br_2-BCP with Raney Ni and ethylenediamine (EDA) under an atmosphere of hydrogen cleanly afforded the desired BCP **(±)-21** in 75% yield. The less reactive Raney Co was also proficient for this transformation,[44] although the reaction was slower and proceeded in lower yield. Treatment of **(±)-21** with TFA afforded free acid **(±)-22** as a crystalline solid.

Bridge Functionalization via Monobromide BCPs: With a reliable method to access mono-brominated BCP **(±)-21**, we next pursued bridgehead derivatives with functionality shown to be compatible with late-stage 2-position derivatization (Figure 5). Recently it has been shown that diester monobromide BCPs are competent substrates for functionalization at the BCP bridge position using metallaphotoredox catalysis.[36] Exposing bromo BCP **(±)-21** to oxidative cleavage conditions yielded the C3 carboxylic acid, with subsequent esterification directly affording the unsymmetric diester **(±)-23** (Figure 5A). In this case, orthogonality between the two esters enables sequential modification at each bridgehead position, allowing for modular access to the litany of manipulations already established in the literature.[45]

Additionally, it has been shown that monobromo BCPs adorned with methoxymethyl (MOM) ether substituents at both bridgehead positions are amenable to lithiation due to coordinative stabilization of the BCP alkyl lithium species, which can be further trapped with electrophiles.[37] Reduction of the *tert*-butyl ester in bromo BCP **(±)-21** and subsequent protection of the resultant alcohol gave unsymmetric bromo BCP **(±)-24**, bearing a single bridgehead MOM ether functionality, also accessible on multi-gram scale. Lithiation of our unsymmetric substrate **(±)-24** using modified literature conditions (Figure 5A)[37] followed by trapping with electrophiles gratifyingly afforded derivatized products **(±)-25a-e** (34–74% yields) bearing diverse substituents (alcohol, ester, ketone, Bpin and amine). Compatibility of the unsymmetric bromo BCP **(±)-24** with the lithiation chemistry demonstrates that modification can be performed with only a single MOM chelating group. Therefore, programmed orthogonality can be leveraged to avoid laborious functional group manipulations to desymmetrize the bridgehead positions for further functionalization, allowing for a streamlined synthetic route forward. Indeed, 2-position ester derivative **(±)-25b** was successfully MOM deprotected and oxidized to carboxylic acid **(±)-26** (Figure 5B).[46] Subsequent decarboxylation afforded 1,2-disubstituted BCP **(±)-27**,[47] a scaffold of interest as an *ortho*- or *meta*-substituted benzene ring bioisostere.[4, 36, 46]

Electrochemical Arylation of Br_2-BCPs: Alkyl bromide functional handles are widely utilized in cross-electrophile couplings (XEC) – particularly in the formation of $C(sp^3)$–$C(sp^2)$ linkages.[48] Nickel electrocatalytic cross-couplings have proven to be suitable for scale-up and have high functional group tolerance and chemoselectivity,[49-51] and due to the limited synthetic methods available for the C2 arylation of BCPs,[19, 36, 46] we envisioned the reductively labile bromide

moiety would provide a convenient handle for derivatization in this manner. The *gem*-Br_2 BCP **2a** exhibits a significantly more positive reduction potential compared to Br-BCP **(±)-21** (see SI for cyclic voltammetry), making it a more suitable precursor for XEC reactions. We hypothesized that electrocatalytic cross-coupling could provide a streamlined route to C2 mono functionalization, as a single set of conditions could allow for arylation followed by reduction of the remaining C–Br bond, eliminating the need for a second reductive process.

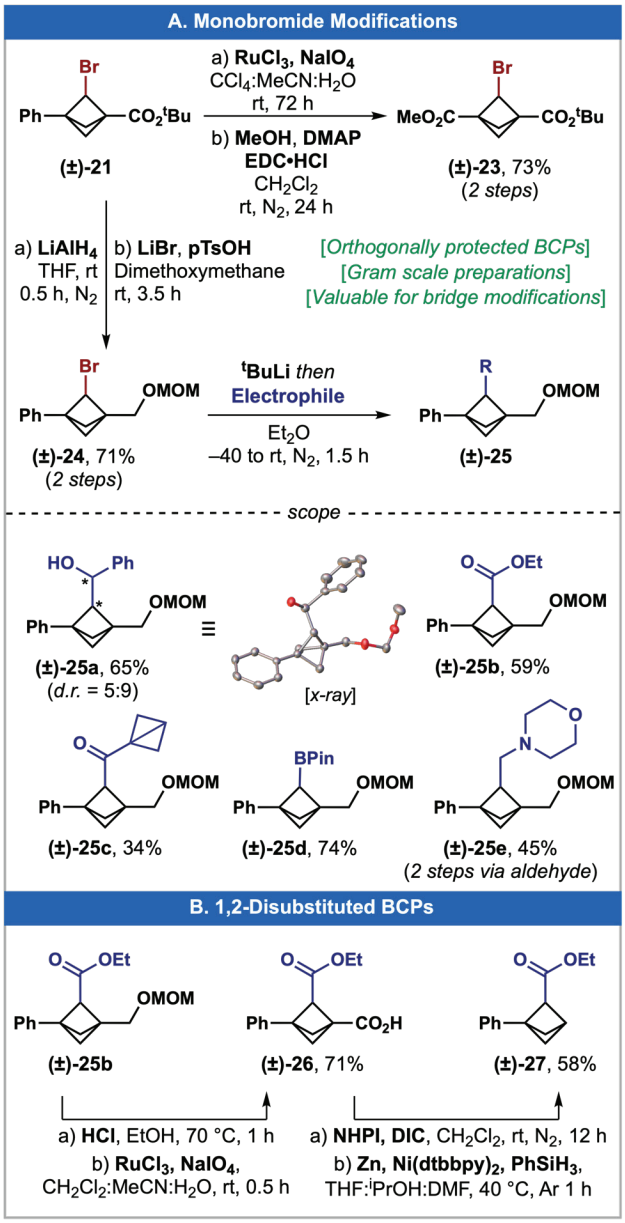


Figure 5. A: Bridgehead modifications of monobromide BCP **(±)-21** and bridge derivatization *via* lithiation of monobromide BCP **(±)-24**. B: Decarboxylative approach to 1,2-disubstituted BCP **(±)-27**.

In its currently realized form, nickel electrocatalytic cross-coupling of BCP **2a** with heteroaryl bromides and iodides (**28**) affords the doubly reduced, singly arylated BCPs **(±)-29a-c** (14–37% yields) (Figure 6). The coupling reactions use inexpensive $NiCl_2$•$6H_2O$ and bipyridine to form the catalyst and trifluoroacetic acid (TFA) and AgOTf as additives. Silver salts and Brønsted acids have previously been shown to be effective additives in nickel electrocatalytic cross couplings.[51, 52] Control experiments highlighted the necessity of nickel, ligand, electricity, and silver and TFA as crucial additives (see SI for details).

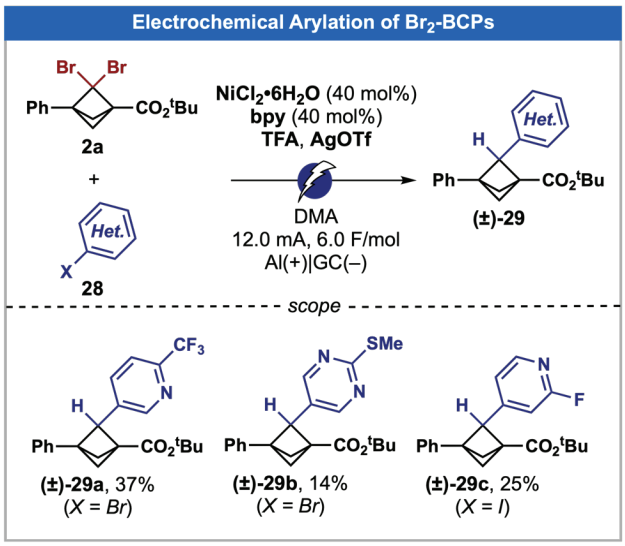


Figure 6. Nickel electrocatalytic cross-coupling of Br_2-BCPs with heteroaryl bromides and iodides.

CONCLUSION

In summary, we demonstrate the first synthesis of a novel suite of bridge-functionalized Br_2-BCPs in an operationally simple and scalable procedure. These compounds further expand the chemical space surrounding BCPs and offer favorable synthetic routes towards bridgehead substituted BCPs for both medicinal and process chemists. Importantly, the reported protocols circumvent the reliance on [1.1.1]propellane as an essential synthetic precursor. Furthermore, we demonstrate that these compounds provide a valuable new route to unsymmetric monobromide BCPs for late-stage modification of the BCP bridge positions and provide proof-of-principle that *gem*-Br_2 BCPs can serve as reductively labile precursors for electroreductive XEC. We therefore envisage that this easily scalable process will enhance access to structurally diverse BCPs, fueling their broader application in both academia and industry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information contains all experimental procedures, analysis, compound characterization data and spectra (PDF).

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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