Organometallic Bridge Diversification of Bicyclo[1.1.1]pentanes

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Abstract: Bicyclo[1.1.1]pentane (BCP) derivatives have attracted significant recent interest in drug discovery as alkyne, *tert*-butyl and arene bioisosteres, where their incorporation is frequently associated with increased compound solubility and metabolic stability. While strategies for functionalisation of the bridgehead (1,3) positions are extensively developed, platforms allowing divergent substitution at the bridge (2,4,5) positions remain limited. Recent reports have introduced 1-electron strategies for arylation and incorporation of a small range of other substituents, but are limited in terms of scope, yields or practical complexity. Herein, we show the synthesis of diverse 1,2,3-trifunctionalised BCPs through lithium-halogen exchange of a readily accessible BCP bromide. When coupled with medicinally relevant product derivatisations, our developed 2-electron "late stage" approach provides rapid and straightforward access to unprecedented BCP structural diversity (>20 hitherto-unknown motifs reported). Additionally, we describe a method for the synthesis of enantioenriched "chiral-at-BCP" bicyclo[1.1.1]pentanes through a novel stereoselective bridgehead desymmetrisation.

The drive to "escape from flatland"[1] in drug discovery has been accelerated by recent advances in the synthetic chemistry of bicyclo[1.1.1]pentanes (BCPs) and other saturated, small-ring bioisosteres of aromatic rings.[2] There are now multiple examples where the incorporation of BCPs into drug-like compounds positively impacts key properties such as solubility, metabolic stability, and propensity towards non-specific binding.[2a,3] While diversely functionalised bridgehead-substituted BCPs (replacements of mono- and *para*-disubstituted arenes) are readily accessible, bridge-substituted BCPs, as potential replacements for *ortho*/*meta*-substituted arenes, remain more challenging to synthesise. While some strategies suffer from restrictions on compatible substrates,[4] others lack divergency since the bridge substituent is introduced at an early stage with limited opportunity for further bridge manipulation.[2g,5] Three recent reports, including our own previous work, show initial examples of divergent synthesis, all using BCP bridge radicals as the key reactive intermediate on account of their kinetic stability and accessibility under mild conditions. Baran showed the synthesis of BCP bridge carboxylic acids, their activation as redox-active esters (**I**), and subsequent application in thermal Negishi-type cross-coupling reactions with benzenoid arylzinc reagents (alongside isolated examples of C–S and C–B cross-coupling reactions) (**Figure 1**, **(a)**).[6] We then showed the direct photochemical decarboxylative Minisci-type reaction of free carboxylic acids (**II**) through *in situ* iodine(III) activation, allowing incorporation of various nitrogen heterocycles through formal arene C–H functionalisation (**Figure 1**, **(b)**).[7] Concurrently, MacMillan investigated a controlled synthesis of a BCP bridge mono-bromide (**III**), which provided a BCP radical upon bromine abstraction by silicon-centered radicals generated under photoredox conditions (halogen atom transfer (XAT)) (**Figure 1**, **(c)**). The generated radicals were then applied to C–C and C–N coupling procedures through metal-mediated reaction with (hetero)aryl bromides and acidic nitrogen nucleophiles, respectively.[8] While these three advances are important, the range of functionality that can be introduced onto BCP bridge positions in a divergent fashion remains limited. Particularly, strategies allowing incorporation of sp^3 carbon, arenes from aryl chlorides, and a broader range of heteroatoms, have until now remained elusive.

An alternative strategy for BCP bridge diversification would be anionic functionalisation. The high *s* character of carbon orbitals used for exocyclic bonding on the bridgehead and bridge positions (~sp^2 and ~$sp^{2.5}$, respectively) renders the BCP core electron-withdrawing and provides a degree of anion stabilisation, consistent with other small-ring systems such as cyclopropanes[9] and bicyclo[1.1.0]butanes.[10] However, essentially all preparatively useful anionic reactions to date have been at the bridgehead positions only. One of several ways[11] to access BCP bridgehead anions is lithium-halogen exchange, principally by treatment of widely accessible BCP iodides with ^{t}BuLi (limited examples using ^{n}BuLi,[12] ^{s}BuLi[13] and LiDBB[14] have also been reported). Extensive data for this lithiation and subsequent reaction with electrophiles have been tabulated.[11] Lithiation at the bridgehead is sometimes associated with expulsion of the group on the other side to form [1.1.1]propellane in a net elimination reaction. Lithiation of a smaller number of BCP bridgehead *bromides* with ^{t}BuLi,[15] and one isolated example

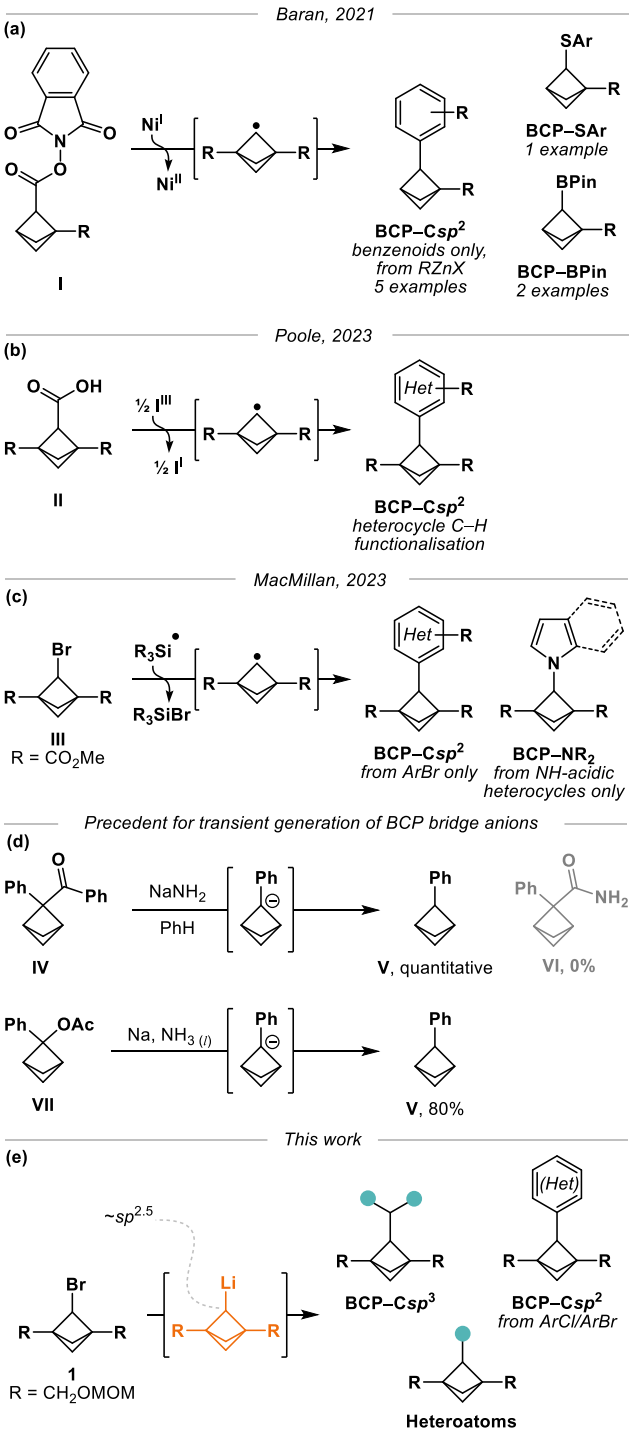
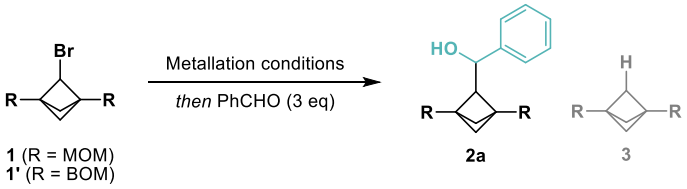


Figure 1. (a)-(c) Selected previous approaches to bridge-substituted BCP derivatives. (d) Precedent for the formal generation of anions on BCP bridge positions. (e) This work.

using MeLi,[16] have also been reported. However, to our knowledge, there are no examples of the corresponding reactions at the BCP *bridge* positions, likely due to poor accessibility of the appropriate halide precursors.[2a] Anionic chemistry at BCP bridge positions in fact appears to be limited to only two proposed benzylic examples (**Figure 1**, **(d)**). The extent to which the aromatic ring offers stabilization to the anion is unclear: the BCP core is reluctant to engage in π-bonding due to increased ring strain, yet Haller-Bauer reaction of **IV** nonetheless provides hydrocarbon **V** rather than carboxamide **VI** arising from alternative collapse of the tetrahedral intermediate. Herein, we show the lithium-halogen exchange of unstabilised BCP bromides and the diverse synthetic utility of the resulting organometallic intermediates ("BCP-Li"). To our knowledge, over 20 of the functionalities installed have yet to be reported on the bridge position of BCPs, and as such this chemistry represents a significant expansion in accessible chemical space.

Initial attempts to metallate **1** or **1'** through direct Mg insertion (**Table 1**, entry 1) or reaction with ^{i}PrMgCl•LiCl, ^{n}Bu$_3$MgLi or MeLi (entries 2-4) under standard conditions were unsuccessful, with unreacted starting material cleanly recovered in each case. Treatment with ^{s}BuLi at either −78 °C or −40 °C, in both the presence and absence of TMEDA (entries 5-8), was similarly ineffective. At −78 °C, even ^{t}BuLi was insufficiently reactive to effect the desired metallation (entry 9). However, we were pleased to find that reaction at −40 °C for 25 minutes enabled complete metallation, providing alcohol **2a** in up to 72% yield following benzaldehyde quench (entry 10). The remaining mass balance was distributed between protodehalogenated BCP **3**, presumably arising from the presence of adventitious water, and small amounts of various unidentified BCP decomposition products.

Table 1. Metallation of bromides **1/1'**.



Entry	R	Metallation conditions	Yield (%)[a]
1	CH_2OBOM	Mg^0, THF, RT[b]	0
2	CH_2OBOM	^{i}PrMgCl•LiCl, THF, 0 °C	0
3	CH_2OMOM	^{n}Bu$_3$MgLi, THF, 0 °C	0
4	CH_2OMOM	MeLi, Et_2O, −40 °C	0
5	CH_2OMOM	^{s}BuLi, Et_2O, −78 °C	0
6	CH_2OMOM	^{s}BuLi, Et_2O, −40 °C	0
7	CH_2OMOM	^{s}BuLi + TMEDA, Et_2O, −78 °C	0
8	CH_2OMOM	^{s}BuLi + TMEDA, Et_2O, −40 °C	0
9	CH_2OMOM	^{t}BuLi, Et_2O, −78 °C	0
10	CH_2OMOM	^{t}BuLi, CPME, −40 °C	70%,[c] 72%[d]

[a] Isolated yield. [b] Magnesium turnings were ground to expose fresh metal surface before use, then further activated *in situ* with DIBAL-H then elemental iodine. [c] 0.101 mmol scale. [d] 3.1 mmol scale.

Having identified these uniquely effective conditions for the desired metallation, we assessed the scope of electrophiles that could be introduced (**Figure 2**). A range of carbonyl electrophiles reacted smoothly to provide the corresponding BCP aldehyde, ester and ketone in synthetically useful yields (**2b**-**2d**). Pre-treatment of the lithiated BCP with commercially available $LaCl_3$•2LiCl solution provided convenient means for reaction with carbonyl compounds bearing acidic α-protons (**2e** and **2f**), avoiding the non-trivial drying[17] of alternative reagents such as $CeCl_3$ and handling of the resulting hygroscopic anhydrous salts. Transmetallation of the BCP-Li to copper, forming either a putative homocuprate (R_2CuLi) or heterocuprate (RCu(CN)), enabled alkylation reactions through both conjugate addition (**2g**) and S_N2 displacement pathways (**2h** and **2i**). The high reactivity of the BCP-Li was highlighted by the fact that attempted reaction with methyl iodide in the absence of copper resulted exclusively

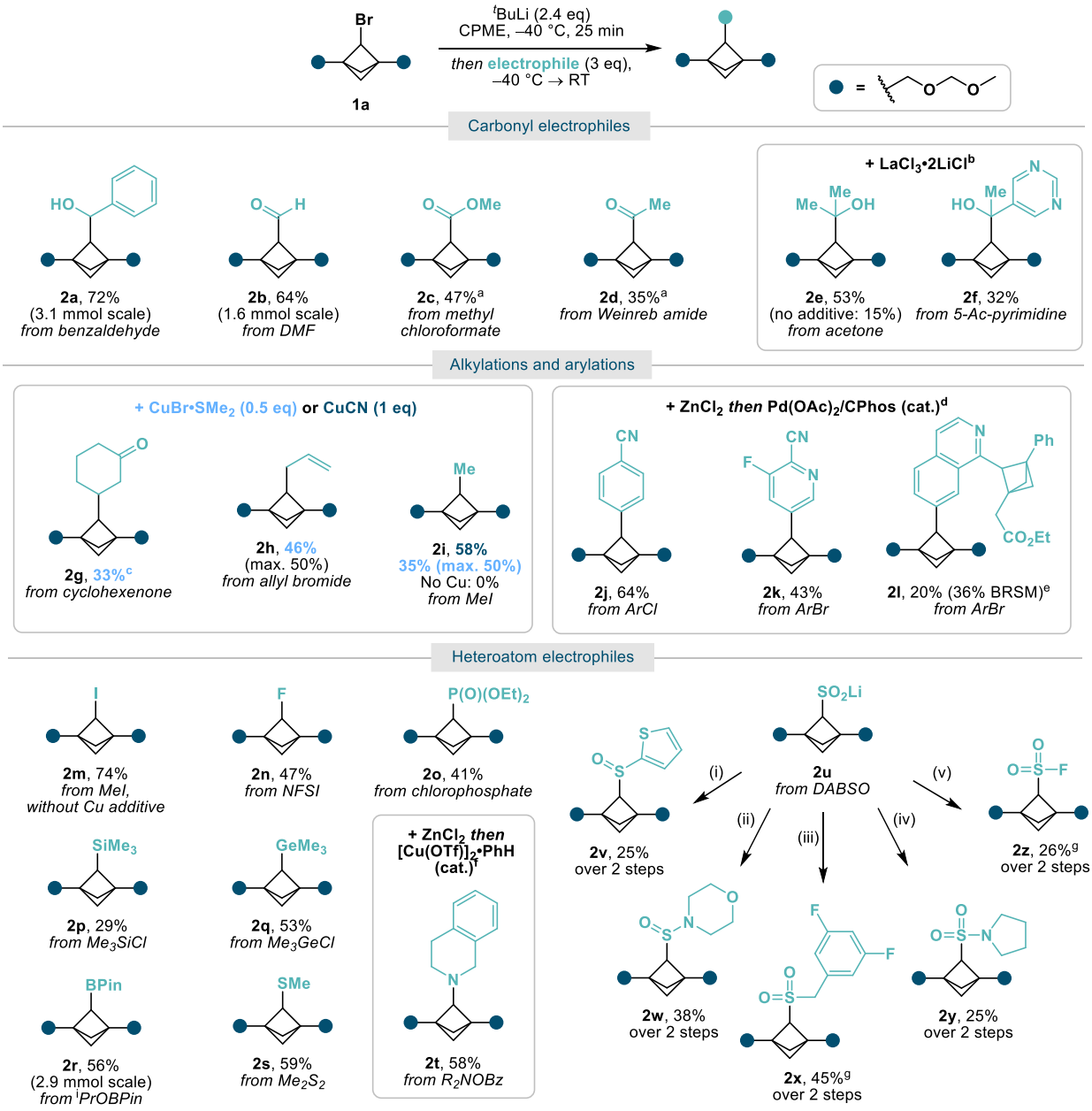


Figure 2. Reaction scope; isolated yields reported from reactions on approximately 0.1 mmol scale. DMF = *N*,*N*-dimethylformamide. NFSI = *N*-fluorobenzenesulfonimide. DABSO = 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct. [a] Reaction mixture further cooled to −78 °C before addition of the electrophile. [b] THF solvent; reaction mixture further cooled to −78 °C before addition of $LaCl_3$•2LiCl. [c] Yield based on enone charged as limiting reagent. [d] Yield based on aryl halide charged as limiting reagent. Lithiation conducted using CPME as solvent; cross-coupling conducted using CPME:THF:toluene as solvent. [e] 41 µmol scale. [f] Lithiation and cross-coupling conducted using THF as solvent. Yield based on R_2NOBz charged as limiting reagent. 2.0 eq ^{t}BuLi charged. [g] Lithiation conducted using Et_2O as solvent. **Reagents for sulfinate derivatisations**: (i) Me_3SiCl *then* 2-thienylmagnesium bromide; (ii) $SOCl_2$ *then* morpholine; (iii) solvent exchange to DMF, then 1-(bromomethyl)-3,5-difluorobenzene, TBAI; (iv) SO_2Cl_2 *then* pyrrolidine; (v) solvent exchange to MeCN:^{i}PrOH (1:1) *then* NFSI.

in a second lithium-halogen exchange to afford BCP iodide **2m** in 74% yield and, presumably, methyllithium. This high-yielding bromine-to-iodine exchange potentially opens opportunity to apply other powerful modern XAT methodologies for decoration of the BCP core.[18] The lower yield of conjugate addition product **2g** may be due to instability of the assumed intermediate Cu-olefin π-complex, since a mixture of unidentified olefinic BCP ring-opened products was also isolated from the reaction mixture (not observed with other electrophiles).

Treatment of the lithiated BCP with 1 eq $ZnCl_2$ to provide an assumed monoorganozinc species (RZnCl) enabled efficient Pd-catalysed Negishi coupling at room temperature with an aryl chloride and functionalised heteroaryl bromides in 64% and 46%/20% yield respectively (**2j**-**2l**).[19] To our knowledge, these transformations represent the first successful examples of palladium-mediated reactions, and 2-electron cross-coupling reactions, reported on BCP bridge positions. By comparison, attempted Negishi coupling with a heteroaryl bromide at room temperature under nickel catalysis[20] gave no detectable product by LCMS analysis. The recommended maximum handling temperature of bromide **1** is 30 °C based on differential scanning calorimetry (DSC) analysis (see ESI), and so transformations of this compound or the derived 2-lithiated intermediate should not exceed this temperature.

A range of heteroatom electrophiles also proved to be suitable: NFSI, diethyl chlorophosphate, Me_3SiCl, Me_3GeCl, ^{i}PrOBPin and Me_2S_2 all afforded the corresponding trisubstituted BCP products (**2n**-**2s**) in moderate to good yields. To our knowledge, BCPs bearing phosphorus, silicon, germanium or aliphatic thioether substituents at the bridge position are all currently absent in the literature. Additionally, the facile synthesis of BCP mono-fluoride **2n** should be compared with the only practical alternative to access this motif, which is the addition of bromofluorocarbene to arene-substituted bicyclo[1.1.0]butanes followed by Raney®-Nickel hydrogenolysis.[4c] Treatment of the lithiated BCP with 0.5 eq $ZnCl_2$ to form a putative diorganozinc (R_2Zn) species, followed by reaction with an *O*-benzoylhydroxylamine under copper catalysis, enabled C–N bond formation in 58% yield (**2t**). This result is notable since existing BCP bridge C–N cross-coupling approaches are limited to the use of acidic nitrogen heterocycle nucleophiles only.[8] Finally, the lithiated BCP was trapped with DABSO to provide BCP sulfinate **2u**, which served as a common precursor to BCP sulfoxide **2v**, sulfinamide **2w**, sulfone **2x**, sulfonamide **2y** and sulfonyl fluoride **2z** through a series of straightforward one-pot procedures (formal 3-component assembly processes). Thus, through the same general lithiation/trapping approach, sulfur(II), sulfur(IV) and sulfur(VI) functionalities are all readily accessible with a high degree of flexibility over the other carbon/nitrogen substituent introduced. Access to BCP **2z** is particularly significant owing to the broad utility of sulfur(VI) fluorides as reagents for covalent protein modification at several nucleophilic amino acid residues (sulfur(VI) exchange/"SuFEx"), with potential applications in the discovery of covalent inhibitor drugs, bioconjugation reactions and chemoproteomic profiling.[21]

The lithiated BCP was also quenched with Ellmann-type sulfinimine **4** to provide sulfinamide **5** as a separable 3:1 mixture of diastereomers (**Figure 3**, **(a)**). The identity of the major diastereomer is assigned based on the open/non-chelated transition state model proposed in the literature for the addition of organolithium reagents to sulfinimines in ethereal solvents.[22] Unexpectedly, acidic cleavage of the auxiliary on each diastereomer (**Figure 3**, **(b)**) was associated with selective hydrolysis of a single MOM group, resulting in bridgehead desymmetrisation and consequent establishment of a new stereogenic centre on the BCP bridge carbon. However, the obtained amino alcohols (**6**) were each found to be single diastereomers (and enantiomers of each other – consistent ^{1}H/^{13}C NMR spectra but opposite optical rotation), indicating that the specific MOM group hydrolysed in each case was controlled, such that the absolute stereochemistry on the BCP core was also controlled. To our knowledge, this represents only the second reported reaction capable of delivering enantioenriched "chiral-at-BCP" bridge-substituted bicyclo[1.1.1]pentanes,[5b] and the first example to do so through late-stage bridgehead desymmetrisation.

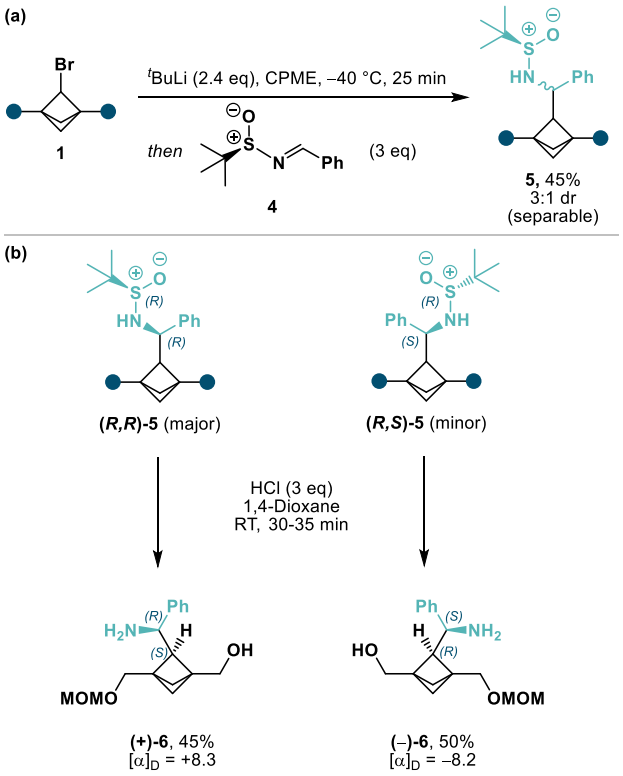


Figure 3. (a) Synthesis of sulfinamide **5**. (b) Attempted deprotection of the sulfinyl moiety in diastereomers of **5**, and observation of concomitant diastereoselective hydrolysis of single bridgehead MOM ether groups.

We rationalise this diastereoselective hydrolysis through neighbouring group participation/stereochemical relay by the NH_2 functionality after liberation from the auxiliary. As shown for the amine derived from major diastereomer **(*R*,*R*)-5** (**Figure 4**, **(a)**), conformations of type I, in which the aromatic ring is extended away from the BCP core, are favoured over conformations of type II in which the two moieties are partially eclipsed. In the calculated lowest-energy conformation of this amine (**(b)**) (see ESI), the distance between the liberated NH_2 group (protonated under the acidic reaction conditions) and both oxygen atoms of the MOM group on the near side of the BCP (as drawn) is <2.5 Å. Thus the NH_2/NH_3^+ group preferentially assists hydrolysis of this MOM group over the other, and *vice versa* for the corresponding enantiomeric amine derived from **(*R*,*S*)-5** (see ESI). This assistance could be through intramolecular protonation (**Figure 4**, **(c)**), and/or through formation of a transient 7-membered hemiaminal ether (**(d)**). In any case, diastereoselective neighbouring group participation accounts for why hydrolysis of one MOM group was found to be significantly faster than the second (only trace amounts of amino-diol observed by LCMS analysis). The remaining mass balance in these reactions was distributed among other partially hydrolysed compounds (sulfinamide cleavage with retention of both MOM groups; mono-MOM cleavage with retention of the sulfinamide; and a pseudo-dimeric bis-BCP acetal compound); and traces of various unidentified degradation products (see ESI for further details).

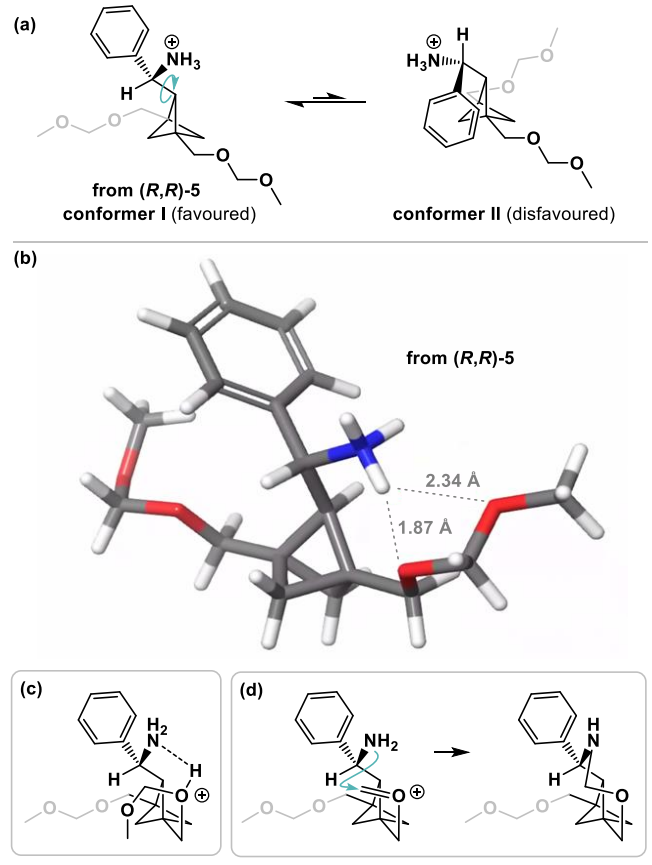


Figure 4. (a) Low- and high-energy conformations of the intermediate amine derived from hydrolysis of **(*R*,*R*)-5**. (b) Calculated (DFT, B3LYP-D3/6-31G+**) lowest-energy conformer of the intermediate amine derived from **(*R*,*R*)-5**. (c) and (d) Potential modes of neighbouring group participation by the NH_2/NH_3^+ group to assist MOM hydrolysis.

At this point, we also sought to confirm that the BCP bridgehead positions could be returned to the carboxylic acid oxidation level and desymmetrised here also. Compound **2a** was selected as a representative example after oxidation to aryl ketone **7** (**Figure 5**, **(a)**). Exposure of **7** to hydrochloric acid with careful control over reaction time allowed isolation of both **8** and unsymmetrical compound (±)-**9**. Diol **8** was then converted into diester **11** under standard conditions, which duly provided unsymmetrical BCP (±)-**12** in 57% yield on treatment with substoichiometric NaOH. Diacid **10** and unreacted diester **11** were also recovered efficiently for re-processing. We note that BCP mono-esters of the same general structure as **12** have been used extensively in the literature for further bridgehead desymmetrisation (see examples, **Figure 5**, **(b)**).

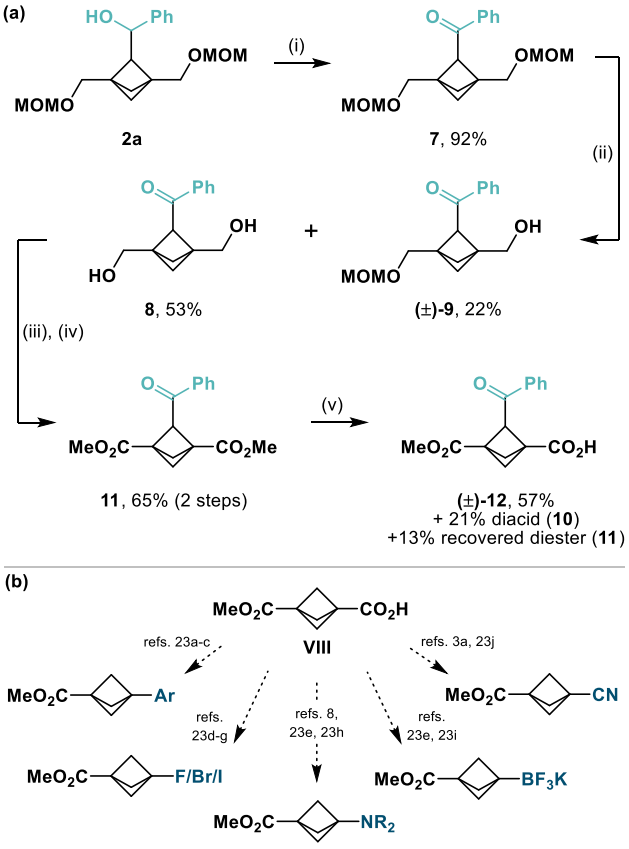


Figure 5. (a) Bridgehead desymmetrisation of aryl ketone **7** to compounds **8** and (±)-**9**, then conversion of **8** to **(±)-12**. (b) Selected reactions reported in the literature for manipulation of BCP mono-esters of general structure **VIII**.[3a,8,23] Reagents and conditions: (i) Dess-Martin periodinane, CH_2Cl_2, RT; (ii) $HCl_{(aq)}$, MeOH, 65 °C; (iii) $RuCl_3$•xH_2O (cat.), $NaIO_4$, CH_2Cl_2/MeCN/H_2O, RT; (iv) EDC•HCl, DMAP, MeOH, CH_2Cl_2, RT; (v) NaOH, MeOH/TBME, RT.

Finally, a range of medicinally relevant derivatisations were explored on the bridge position to highlight the synthetic potential of selected BCP products. Ester **2c** was converted into cyclopropanol **13** in synthetically useful yield under Kulinkovich conditions (**Figure 6, (a)**). α,β-Unsaturated ester **14**, amine **15**, triazole **16** and oxazolidinone **17** were readily accessible from aldehyde **2b** in 1-3 steps. Finally, oxidation of boronate **2r** afforded alcohol **18** in excellent yield (**Figure 6, (c)**). Treatment of **18** with Me_3OBF_4[5b] provided methyl ether **19** in excellent yield, representing, to our knowledge, the first reported successful alkylation reaction of a BCP bridge alcohol.

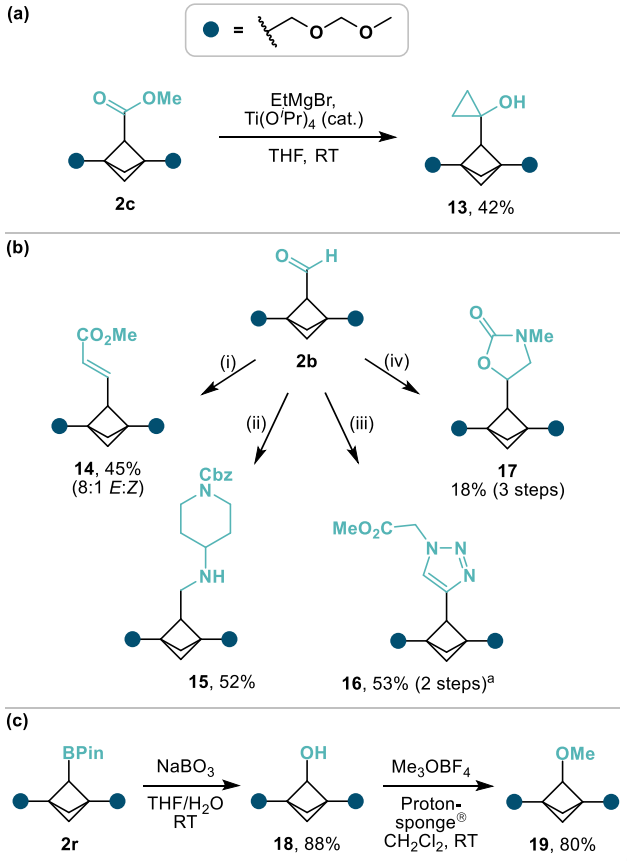


Figure 6. Derivatisations of compounds **2b**, **2c** and **2r**. Reagents and conditions: (i) methyl (triphenylphosphoranylidene)acetate, THF, 50 °C; (ii) benzyl 4-aminopiperidine-1-carboxylate, picoline-borane, MeOH/AcOH, RT; (iii) 1st step: Bestmann-Ohira reagent, K_2CO_3, MeOH, RT. 2nd step: methyl azidoacetate, $CuSO_4$•$5H_2O$, sodium ascorbate, ^{t}BuOH/H_2O, RT; (iv) 1st step: $Me_3S^+I^-$, KOH, MeCN/H_2O, 60 °C. 2nd step: $MeNH_2$, MeOH, 85 °C (microwave). 3rd step: CDI, DMAP, THF, RT. [a] Isolated as a 3:1 mixture with the corresponding carboxylic acid due to partial ester hydrolysis during concentration of aqueous fractions from preparative HPLC purification. Yield is calculated without consideration of this hydrolysis.

In summary, we present a procedure for BCP bridge metallation/electrophilic trapping which provides significant expansion of accessible BCP chemical space. This rapid diversification strategy is complementary to previous 1-electron approaches, and allows modern practitioners to capitalize on the significant volume of historical literature on classical organolithium reactions. An unexpected diastereoselective bridgehead desymmetrisation reaction was also discovered which enables control of the absolute stereochemistry at the BCP bridge. This could provide a starting point for future work into more general auxiliary-based asymmetric desymmetrisation methodologies. While we acknowledge that ^{t}BuLi requires particular care during use, it can be handled safely by competent users and is uniquely effective for this metallation. With further research, continuous flow technology,[24] the use of deep eutectic solvents,[25] or stabilizing organogels,[26] may provide attractive solutions for further scale-up.

Supporting Information

The authors have cited additional references within the Supporting Information.

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Keywords: bicyclo[1.1.1]pentanes • lithiation • bioisosteres • strained molecules • small-ring systems

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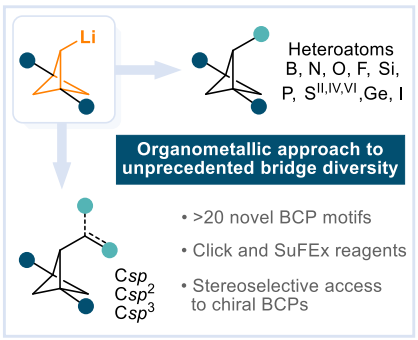

Text for Table of Contents: Lithium-halogen exchange of a BCP bridge bromide is reported, which upon electrophilic quench provides unprecedented structural diversity on this privileged arene bioisostere. The method is complementary to previous radical diversification methods and allows application of the wealth of organolithium literature to this current “hot topic” synthetic problem. A method of controlling the absolute stereochemistry on the BCP bridge position, through a diastereoselective bridgehead desymmetrisation, is also shown.

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