

# Bridge Cross-Coupling of Bicyclo[1.1.0]butanes

Ryan E. McNamee, Ayan Dasgupta, Kirsten E. Christensen, and Edward A. Anderson\*



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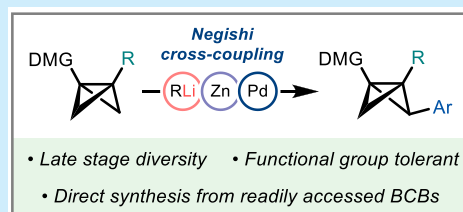
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**ABSTRACT:** Bicyclo[1.1.0]butanes (BCBs) have gained growing popularity in “strain release” chemistry for the synthesis of four-membered-ring systems and *para*- and *meta*-disubstituted arene bioisosteres as well as applications in chemoselective bioconjugation. However, functionalization of the bridge position of BCBs can be challenging due to the inherent strain of the ring system and reactivity of the central C–C bond. Here we report the first late-stage bridge cross-coupling of BCBs, mediated by directed metalation/palladium catalysis.

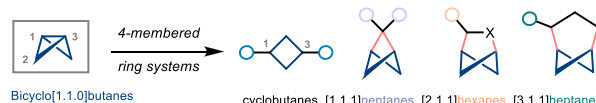


Bicyclo[1.1.0]butanes (BCBs) (Figure 1a) are a class of highly strained hydrocarbons that have become valuable tools for “strain release” chemistry.<sup>1</sup> These reagents possess the impressive ability to react with nucleophiles,<sup>2</sup> radicals,<sup>3</sup> electrophiles,<sup>4</sup> and transition metal catalysts,<sup>5</sup> with applications ranging from the synthesis of natural products<sup>2d</sup> and *para*-<sup>6</sup> and *meta*-substituted<sup>7</sup> arene bioisosteres to use as cysteine-selective bioconjugation agents.<sup>2b,8</sup> Access to these building blocks has been streamlined with the recent developments of late-stage bridgehead and bridge metalation protocols that deliver a broad portfolio of BCBs,<sup>9</sup> including a convenient one-pot sulfone-based reaction sequence that affords exceptional diversity.<sup>10</sup>

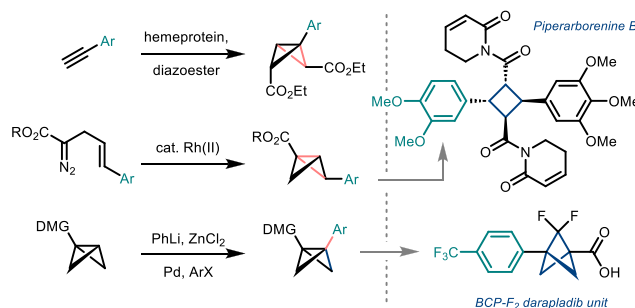
BCBs that are aryl-substituted at the bridge carbon atoms are attractive targets due to their potential use in accessing arene-functionalized products upon ring opening. Specifically, access to these products would open up new avenues for medicinal chemists in bicyclo[1.1.1]pentane, -[2.1.1]hexane, and -[3.1.1]heptane synthesis for reaching novel chemical space.<sup>7b</sup> Recent methodologies developed for the synthesis of aryl-substituted BCBs include (1) biocatalytic double diazo-alkyne condensation that introduces two identical *endo/exo* bridge ester substituents (bridgehead aryl, Figure 1b);<sup>11</sup> (2) asymmetric intramolecular diazo insertion into styrenes, catalyzed by rhodium(II) (bridge aryl);<sup>2e,12</sup> and (3) bridgehead-directed metalation and cross-coupling (bridgehead aryl).<sup>9a</sup> The methods outlined in each case address different challenges, such as the latter providing a divergent synthesis of bicyclopentyl reagents, and the asymmetric diazo insertion facilitating a route toward the total synthesis of piperarborene B.<sup>2d</sup> However, although intramolecular diazo insertion offers a powerful method for asymmetric bridge-arylated BCB synthesis, it suffers from the drawback of synthetic linearity rather than late-stage diversification.

We previously developed a method that enables late-stage bridge functionalization through directed metalation/electrophilic quench,<sup>9b</sup> although this tactic did not enable the introduction of aryl and alkenyl substituents. We questioned

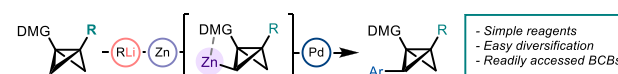
## a) Applications of BCB in Synthesis



## b) Previous work: Aryl BCBs



## c) This work: Bridge Cross-Coupling



**Figure 1.** (a) Applications of BCBs in cyclobutane and bioisostere synthesis. (b) Previous work toward the construction of aryl-substituted BCBs. (c) Bridge directed metalation and cross-coupling of BCBs. DMG = directing metalation group.

whether we might be able to extend this approach to bridge cross-coupling by transmetalation of the intermediate organolithium, enabling the rapid delivery of bridge aryl-substituted

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Table 1. BCB Cross-Coupling Optimization<sup>a</sup>

| entry | [M]                                 | ligand, variation of conditions                                                  | yield (%) <sup>b</sup> |
|-------|-------------------------------------|----------------------------------------------------------------------------------|------------------------|
| 1     | B(OH) <sub>3</sub> (1a)             | PPh <sub>3</sub>                                                                 | 0                      |
| 2     | Sn( <i>n</i> -Bu) <sub>3</sub> (1b) | AsPh <sub>3</sub>                                                                | 0                      |
| 3     | ZnCl <sub>2</sub> -LiCl (1c)        | PPh <sub>3</sub> , TMEDA (1.1 equiv)                                             | 0                      |
| 4     | ZnCl <sub>2</sub> -LiCl (1c)        | PPh <sub>3</sub>                                                                 | 28                     |
| 5     | ZnCl <sub>2</sub> -LiCl (1c)        | CyJPhos                                                                          | 48                     |
| 6     | ZnCl <sub>2</sub> -LiCl (1c)        | CyJPhos, 20 °C                                                                   | 6                      |
| 7     | ZnCl <sub>2</sub> -LiCl (1c)        | CyJPhos, DMF/Tol/1,4-dioxane <sup>c</sup>                                        | — <sup>d</sup>         |
| 8     | ZnCl <sub>2</sub> -LiCl (1c)        | CyJPhos, PhI (4.0 equiv)                                                         | 60                     |
| 9     | ZnCl <sub>2</sub> -LiCl (1c)        | CyJPhos <sub>2</sub> (30 mol %) and Pd(dba) <sub>2</sub> (15 mol %) <sup>e</sup> | 71                     |

<sup>a</sup>Reactions were conducted on a 0.1 mmol scale. See the Supporting Information for details of metalation protocols in the synthesis of 1a–1c.

<sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixtures using 1,3,6-trimethoxybenzene as an internal standard. <sup>c</sup>Heated at 110 °C. <sup>d</sup>Extensive decomposition was observed in these solvents. <sup>e</sup>Stirred for 1 h at room temperature before heating.

strain release reagents (Figure 1c). Notably, a similar strategy has been employed in the elegant polyfunctionalization of cubanes.<sup>13</sup>

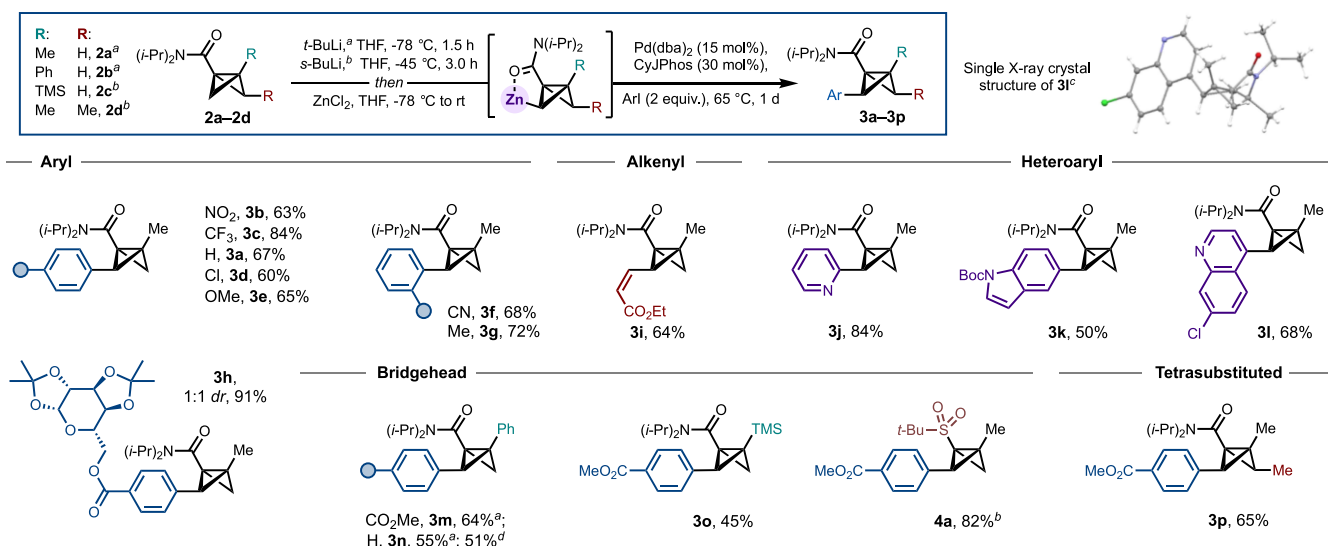
Reaction development began by employing three potential BCB organometallic coupling partners, boronic acid 1a, stannane 1b, and organozinc 1c (prepared from metalation of BCB 2a with organolithiums and electrophilic quench (1a/b) or transmetalation to ZnCl<sub>2</sub> (1c)), in Suzuki, Stille, and Negishi coupling protocols, respectively (Table 1, entries 1–3). Interestingly, the former two strategies led only to complete decomposition of the starting material with no observable product, while entry 3 returned 2a with no sign of degradation. This was surprising given previous reports on cyclopropylzinc Negishi couplings as well as our own work on BCB bridgehead Negishi reactivity,<sup>9a,14</sup> and it was hypothesized that TMEDA might be interfering with the reaction. To our delight, the use of TMEDA-free metalation in the generation of 3a (*t*-BuLi in THF) and submission to equivalent coupling conditions (Pd(dba)<sub>2</sub>/2PPh<sub>3</sub>) achieved cross-coupling in 28% yield (as determined by <sup>1</sup>H NMR spectroscopy; entry 4). A screen of 13 phosphine ligands was conducted, with the Buchwald-based ligands producing the highest yields and CyJPhos being optimal (48%; entry 5).<sup>15</sup> A temperature and solvent screen identified THF at 65 °C as being crucial for this transformation (entries 6 and 7). Increasing the equivalents of iodobenzene led to a further increase in the yield (60%; entry 8). While a useful result, the conversion could be further enhanced by increasing the catalyst loading to 15 mol %, giving 3a in 71% yield (entry 9). On scale-up, it became apparent that stirring the reaction mixture for 1 h at room temperature was crucial; otherwise, the reaction would fail due to Pd black formation.

With optimized metalation and cross-coupling conditions in hand, we then examined the scope of the reaction (Scheme 1). A selection of aryl iodides bearing electron-withdrawing and -donating groups at the *para* position was first investigated. To our delight, these couplings proceeded in good to excellent yields (3a–3e, 60–84%). Reaction efficiency was maintained with *ortho*-substituted aryl iodide derivatives (3f and 3g). The introduction of biorelevant functionality was also possible, for example, incorporating a galactose-bearing side chain in excellent yield (3h, 91%, 1:1 *dr* due to the racemic generation of 1c).

Alkenyl iodides were also compatible with the coupling conditions (3i, 64%); however, alkenes bearing an electron-withdrawing group were essential for the product stability. Heterocycle cross-coupling is also highly appealing from a medicinal chemistry stance due to the application of BCBs in *para*- and *meta*-arene bioisostere synthesis. We were therefore delighted to find that a representative range of azacycles could be installed in good yields (50–84%), including 2-substituted pyridine (3j), indole (3k), and quinoline (3l). Pleasingly, these conditions could also be applied to BCB 2b, which is more sterically demanding at the bridgehead position (Ph substituent), giving 3m (64%) and 3n (55%). The latter coupling was also carried out on a 1 mmol scale without significant detriment to the yield (51%).

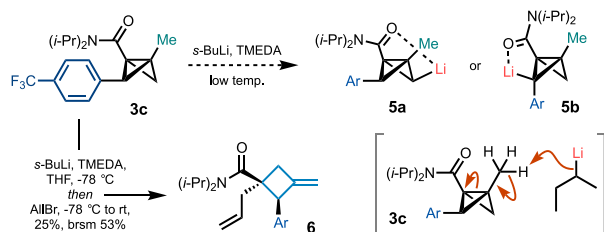
Cross-coupling on other BCBs, such as trimethylsilyl-substituted BCB 2c and trisubstituted BCB 2d would demonstrate the feasibility of constructing more complex derivatives, including a tetrasubstituted product. However, no product was observed when 2c and 2d were subjected to the developed metalation and cross-coupling conditions, with neither undergoing productive metalation with *t*-BuLi at –78 °C in THF. Fortunately, TMEDA-free conditions for directed lithiation were identified (*s*-BuLi at –45 °C in THF)<sup>15</sup> that could be applied to 2c and 2d. These substrates were then subjected to the cross-coupling conditions and, to our delight, produced silyl-substituted BCB 3o in 45% yield and tetrasubstituted BCB 3p in 65% yield. Resolving the cross-coupling issue of 2c and 2d inspired us to examine sulfone substrates; pleasingly, 4a could be obtained in an excellent yield of 82% with the *s*-BuLi metalation conditions.

Having successfully demonstrated cross-coupling with trisubstituted BCB 2d, we questioned whether a complementary approach could be established through a second directed bridge metalation *after* bridge arylation (Scheme 2). BCB 3c was chosen as a candidate, as the bridge arene possesses a *para* electron-withdrawing group (CF<sub>3</sub>) that is tolerant of organolithiums. This substrate presents a regioselectivity challenge: the possibility of directed metalation (5a, Scheme 2) or benzylic deprotonation (5b), both of which would provide a useful class of novel BCBs. Surprisingly, when 3c was subjected to the optimized conditions, neither the unsubstituted bridge nor the benzylic bridge underwent lithiation. Instead, *s*-BuLi was directed to the bridgehead

Scheme 1. Synthesis of Aryl Bridge-Substituted BCBs<sup>c</sup>

<sup>c</sup>Reaction conditions, unless stated otherwise: **2a** or **2b** (0.20 mmol, 1.0 equiv); 1. Lithiation: <sup>a</sup>*t*-BuLi (0.22 mmol, 1.1 equiv, 1.1–1.3 M in pentane, THF,  $-78^\circ\text{C}$ , 1.5 h; <sup>b</sup>*s*-BuLi (0.22 mmol, 1.1 equiv, 1.1–1.5 M in cyclohexane), THF,  $-45^\circ\text{C}$ , 3.0 h; 2. Transmetalation/coupling: ZnCl<sub>2</sub> (0.22 mmol, 1.1 equiv), THF,  $-78^\circ\text{C}$  (or  $-45^\circ\text{C}$ ) to rt; Pd(dba)<sub>2</sub> (15 mol %), CyJPhos (30 mol %), R–I (0.4 mmol, 2.0 equiv) THF, 1 h,  $20^\circ\text{C}$ ; 1 d,  $65^\circ\text{C}$ . <sup>c</sup>Structure of **3l** from single-crystal X-ray diffraction studies (displacement ellipsoids drawn at 50% probability). <sup>d</sup>The reaction was conducted on a 1 mmol scale.

methyl group, which then underwent BCB ring opening to give the corresponding enolate; quenching with allyl bromide afforded polysubstituted exocyclic cyclobutene **6**. This observation of this alternative metalation pathway may relate to restricted rotation of the directing group in substrate **3c**, which prevents access to the unsubstituted bridge, as observed in the X-ray crystal structure of **3l** and <sup>1</sup>H NMR spectrum of the bridge aryl-BCB derivatives.<sup>15</sup>

Scheme 2. Unexpected Fragmentation in the Metalation of Bridge-Arylated BCB **3c**<sup>a</sup>

<sup>a</sup>The reaction was run on a 0.12 mmol scale using optimized conditions with allyl bromide (0.6 mmol, 5.0 equiv) quench.

In summary, we have developed a convenient and general late-stage Negishi cross-coupling strategy to access sp<sup>2</sup>-bridge-substituted BCBs. This approach enables the introduction of arenes, heteroarenes, and alkenes with broad functional group tolerance with respect to the arene: nitro, ester, halide, silyl, nitrile, ether, and acetal groups are all accommodated, which can allow for further manipulation. This approach enables the rapid delivery of new strain release reagents, which we expect to be of use to the wider chemical community for small-ring and bioisostere construction.

## ■ ASSOCIATED CONTENT

## Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

## ■ Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c04030>.

Additional experimental discussion, experimental procedures, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra (PDF)

## Accession Codes

CCDC 2292149 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION

## Corresponding Author

Edward A. Anderson – Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Oxford OX1 3TA, U.K.; [orcid.org/0000-0002-4149-0494](https://orcid.org/0000-0002-4149-0494); Email: [edward.anderson@chem.ox.ac.uk](mailto:edward.anderson@chem.ox.ac.uk)

## Authors

Ryan E. McNamee – Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Oxford OX1 3TA, U.K.

Ayan Dasgupta – Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Oxford OX1 3TA, U.K.

Kirsten E. Christensen – Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Oxford OX1 3TA, U.K.



Complete contact information is available at:  
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## Notes

The authors declare no competing financial interest.

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- (15) See the [Supporting Information](#) for details.