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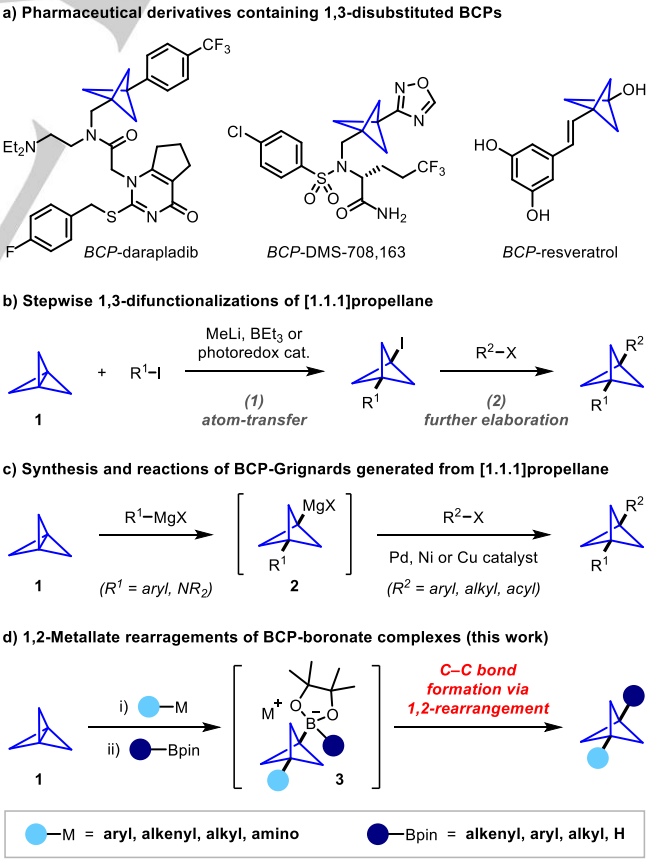
1,3-Difunctionalizations of [1.1.1]Propellane via 1,2-Metallate Rearrangements of Boronate Complexes

Songjie Yu,† Changcheng Jing,† Adam Noble, and Varinder K. Aggarwal*[a]

Abstract: 1,3-Disubstituted bicyclo[1.1.1]pentanes (BCPs) are valuable bioisosteres of *para*-substituted aromatic rings. The most direct route to these structures is via multi-component ring-opening reactions of [1.1.1]propellane. However, challenges associated with these transformations mean that difunctionalized BCPs are more commonly prepared via multistep reaction sequences with BCP-halide intermediates. Herein, we report three- and four-component 1,3-difunctionalizations of [1.1.1]propellane with organometallic reagents, organoboronic esters and a variety of electrophiles. This is achieved by trapping intermediate BCP-metal species with boronic esters to form boronate complexes, which are versatile intermediates whose electrophile-induced 1,2-metallate rearrangement chemistry enables a broad range of C–C bond-forming reactions.

Bicyclo[1.1.1]pentane (BCP) is a highly valuable motif in drug discovery.[1] Its size and conformational rigidity make 1,3-disubstituted BCPs bioisosteres of *para*-substituted benzene rings.[2] Structure activity relationships have shown that incorporating these sp^3-rich surrogates of aromatic rings into drug candidates often results in more favorable pharmacokinetic properties, including improved aqueous solubility, increased membrane permeability, and higher metabolic stability (Scheme 1a).[3] Despite these desirable characteristics, application of 1,3-disubstituted BCP derivatives in drug discovery has been hindered by the limited number of concise synthetic routes to these motifs, in particular carbon-substituted analogues. One of the most powerful approaches to BCPs is via addition reactions to [1.1.1]propellane (**1**),[4] where the central σ-bond can be cleaved under both radical[5] and anionic pathways (Scheme 1b).[6] However, these reactions typically give monofunctionalized BCPs, or involve atom-transfer processes where, in addition to a carbon substituent, a halide group is introduced. Therefore, access to 1,3-disubstituted BCPs with two carbon substituents requires additional manipulations of the halide.[5c–e,7]

Direct transformation of **1** into unsymmetrical 1,3-disubstituted BCP derivatives via three-component coupling reactions is challenging because of competing oligomerization of the intermediate BCP radicals or carbanions.[4d,8] This is especially apparent for radical processes, of which there is only a single report by Uchiyama and co-workers describing a three-component aminoalkylation of **1**.[9] In contrast, BCP-Grignard intermediates **2** are relatively stable to oligomerization with **1** and can be intercepted in palladium- or nickel-catalyzed cross-couplings,[10] copper-catalyzed alkylations,[11] or acylation reactions (Scheme 1c).[10b,10d,11] We were intrigued by the possibility of intercepting BCP-Grignards **2** with boronic esters to form BCP-boronate complexes **3** (Scheme 1d). These versatile intermediates can be utilized in a wide range C–C bond forming reactions via 1,2-metallate rearrangements,[12] therefore providing a significant expansion to the range of unsymmetrical 1,3-disubstituted BCP derivatives accessible in one step from **1**. Herein, we describe the successful realization of this approach in a transition metal-free three-component coupling between organometallic reagents, [1.1.1]propellane, and organoboronic esters. Furthermore, this strategy could be extended to a four-component coupling by trapping alkenyl BCP-boronate complexes with a range of electrophiles, enabling rapid access to highly functionalized BCP-derivatives.



Scheme 1. Synthesis of 1,3-difunctionalized bicyclo[1.1.1]pentanes.

[a] Dr. S. Yu, Dr. C. Jing, Dr. A. Noble, Prof. Dr. V. K. Aggarwal
School of Chemistry, University of Bristol
Cantock's Close, Bristol, BS8 1TS (UK)
E-mail: v.aggarwal@bristol.ac.uk

[†] These authors contributed equally.

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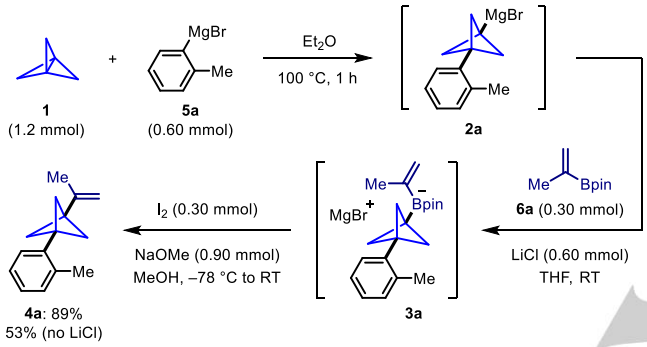
Our initial studies focused on the reaction of BCP-Grignard reagent **2** in Zweifel olefinations with alkenylboronic esters to provide synthetically useful alkenyl-BCPs **4** (Scheme 2).[13] Using conditions developed by Knochel and co-workers,[10d] BCP-Grignard **2a** was conveniently accessed from 2-tolylmagnesium bromide (**5a**) and **1**. Addition of 2-propenylboronic ester **6a** formed boronate complex **3a**, which was subsequently reacted with iodine and sodium methoxide to promote 1,2-migration and boron elimination, yielding alkenyl-BCP **4a** in 53% yield. A recent report by Morken and co-workers found that boronate complex formation between vinyl Grignard reagents and pinacol boronic esters was greatly facilitated by LiCl,[14] which is known to increase the reactivity of Grignard reagents.[15] Pleasingly, addition of LiCl to BCP-Grignard **2a** prior to **6a** resulted in a much improved yield of **4a** of 89%.

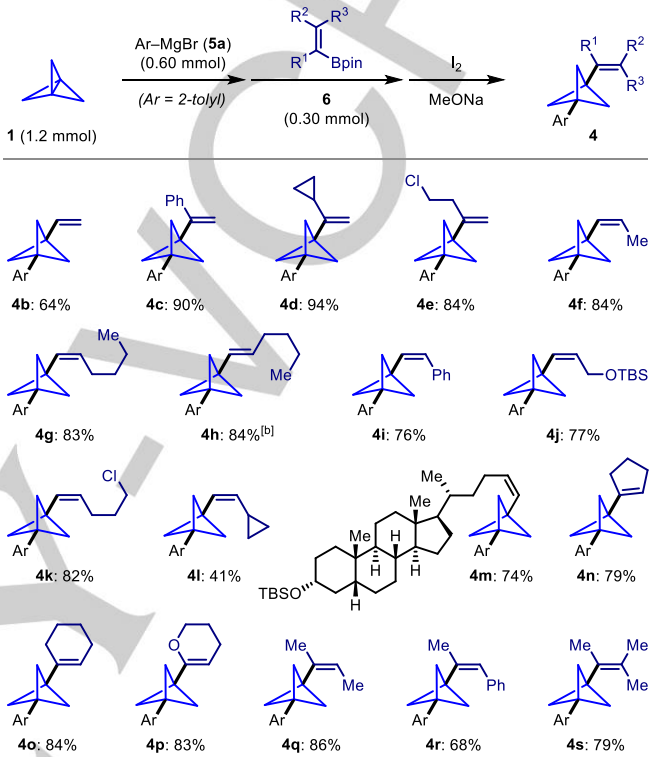


Scheme 2. Initial results for the BCP formation via Zweifel olefination.

With high yielding conditions in hand, we subsequently explored the scope of this three-component coupling (Table 1). Analysis of a range of alkenylboronic esters demonstrated the generality of the protocol, which could be used to access vinyl-BCP **4b** and a range of 1,1-disubstituted alkenes (**4c**–**e**) in good to excellent yields. For *E*-configured β-substituted alkenylboronic esters, Zweifel olefination leads to the corresponding *Z*-alkene products.[13c] This allowed the synthesis of a wide range of *Z*-alkenyl BCP derivatives (**4f**–**g**, **4i**–**m**), all with >95:5 *Z*:*E* selectivity. Conversely, using a *Z*-alkenylboronic ester provided *E*-alkenyl BCP product **4h**, again with excellent yield and stereocontrol (>95:5 *E*:*Z*). The functional group tolerance of the reaction was demonstrated by preparing alkenyl-BCPs containing silyl ethers (**4j**), halides (**4k**), cyclopropanes (**4l**), and complex natural product scaffolds, such as lithocholic acid derivative **4m**. Trisubstituted alkenes were also formed in high yields, including both cyclic (**4n**–**p**) and acyclic (**4q**–**r**) examples, with the latter being formed with excellent stereoselectivity (>95:5 *Z*:*E*). Finally, the Zweifel olefination could also be applied to the high yielding synthesis of tetrasubstituted alkenes (**4s**).

We next examined the scope of the reaction with respect to the organometallic reagent (Table 2). We were pleased to find that a broad range of functionalized aryl Grignards provided aryl-BCP products **4t**–**4ac** in high yields. Alkenyl Grignards were also found to be competent reagents for ring-opening of **1**, providing 1,3-bisalkenyl BCPs **4ad** and **4ae**. To the best of our knowledge, these two examples represent the first reports of ring-opening of **1** with alkenyl Grignard reagents.

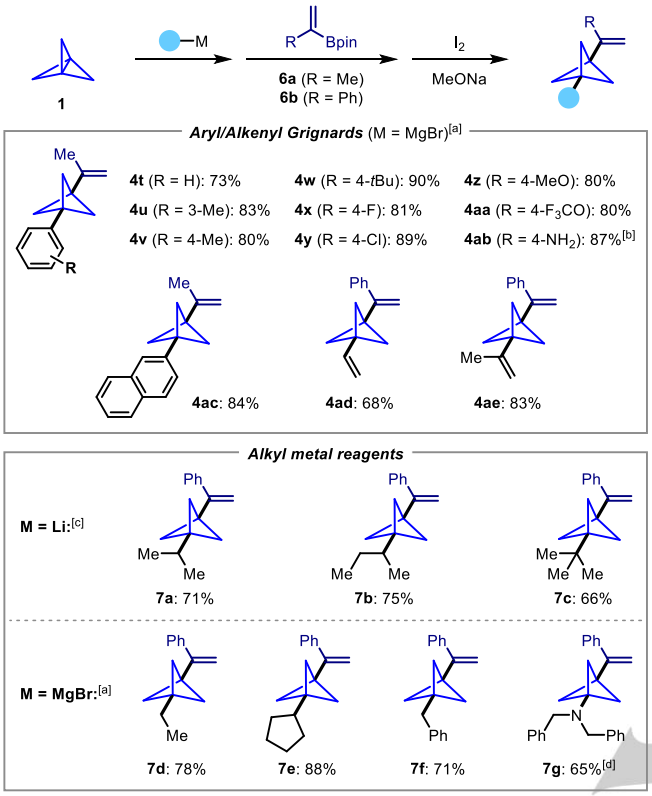
Table 1. Scope of alkenylboronic esters.[a]



[a] Yields are of isolated products. See Scheme 2 for reaction conditions. Products **4f**–**4m** and **4q**–**4r** were formed with >95:5 stereoselectivity. [b] Using (*Z*)-hex-1-en-1-ylboronic acid pinacol ester.

Inspired by previous reports of alkylmetal additions to **1**,[10b,16] we sought to extend this methodology beyond aryl/alkenyl-substituted BCP synthesis. Therefore, we investigated the addition of a range of alkyllithium reagents to **1** and subsequent Zweifel olefination of the resulting BCP-lithium intermediate (Table 2). Secondary and tertiary alkyllithiums reacted efficiently with **1** at –78 °C, with subsequent high yielding Zweifel olefination giving alkyl BCP derivatives **7a**–**7c**. On the other hand, primary alkyllithiums (e.g., *n*BuLi) were unreactive at –78 °C and elevated temperatures led only to polymerization of **1**.[17] Fortunately, the use of primary alkyl Grignards circumvented this issue and enabled formation of ethyl-BCP derivative **7d** in high yield. Grignard reagents could also be used for the introduction of secondary alkyl (**7e**) and benzyl groups (**7f**). Finally, reaction of **1** with the "turbo amide" pioneered by Baran and co-workers provided amino-BCP **7g** in good yield.[6a]

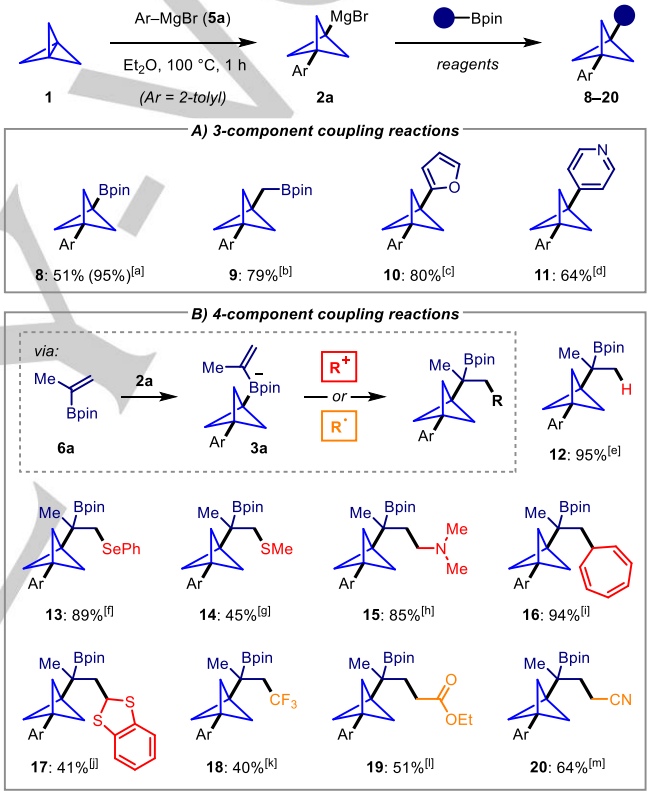
Table 2. Scope of alkylmetal reagents.



[a] Using **1** (1.2 mmol) and Grignard reagent (0.60 mmol) in Et_2O at 100 °C for 1–2 h, then LiCl (0.60 mmol), **6b** (0.30 mmol), I_2 (0.30 mmol) and MeONa (0.90 mmol). [b] Using (4-(bis(trimethylsilyl)amino)phenyl)magnesium bromide. [c] Using **1** (0.30 mmol) and alkyllithium (0.45 mmol) in Et_2O at –78 °C for 30 min, then **6b** (0.45 mmol), I_2 (0.30 mmol) and MeONa (0.90 mmol). [d] Reaction of Bn_2NMgBr•LiCl with **1** was at RT for 16 h.

To extend the range of BCP-derivatives accessible using this 1,2-metallate rearrangement strategy, we investigated the reaction of BCP-Grignard **2a** with a variety of other boronic ester substrates (Scheme 3A). Reaction with pinacolborane provided synthetically useful BCP-boronic ester **8** in moderate yield.[12,18] The low yield is likely a result of the instability of **8** during chromatographic purification, which is supported by isolation of the corresponding alcohol in 95% yield after *in situ* oxidation. Alkylation of **2a** with chloromethylboronic acid pinacol ester gave alkylboronic ester **9** via a Matteson homologation, and arylations of **2a** were possible using our previously reported transition metal-free couplings, forming BCP-furan **10** and BCP-pyridine **11** in good yields.[19]

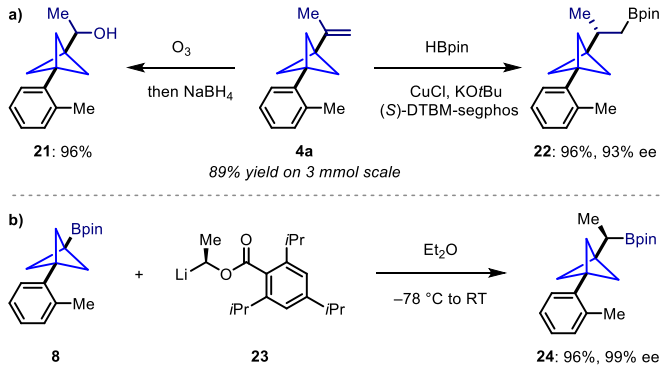
To further demonstrate the diversity of BCP-boronate chemistry for the synthesis of functionalized BCP-derivatives, we extended our approach to four-component coupling reactions (Scheme 3B). Alkenyl BCP-boronate complex **3a**, formed from aryl Grignard **5a**, **1**, and alkenyl boronic ester **6a**, was found to undergo efficient electrophile-induced 1,2-metallate rearrangement with a range of heteroatom- and carbon-based electrophiles under both polar and radical pathways. Electrophiles included tetrafluoroboric acid, providing tertiary boronic ester **12**; and phenylselenyl chloride and dimethyl(methylthio)sulfonium tetrafluoroborate, which gave selenide **13** and sulfide **14**, respectively.[20] Boronate **3a** was successfully alkylated with Eschenmoser's salt, tropylium tetrafluoroborate, and 1,3-benzodithiolylium tetrafluoroborate, forming products **15**–**17**. Finally, alkylation of **3a** with electron-deficient alkyl iodides was possible using our previously reported photochemical conditions,[21] allowing incorporation of trifluoromethyl (**18**), ester (**19**) and nitrile (**20**) groups. Importantly, this four-component coupling reaction provides access to highly functionalized BCP-derivatives containing vicinal quaternary centers; structures that previously could only be accessed via multi-step synthesis.



Scheme 3. Multi-component reactions of BCP-boronate complexes. *Reagents*: [a] HBpin, aq. HCl, yield in parenthesis is of the corresponding alcohol after in situ oxidation with $NaOH/H_2O_2$; [b] $ClCH_2Bpin$; [c] furan-2-yl-Bpin, NBS; [d] pyridin-4-yl-Bpin, $ClCO_2CH_2CCl_3$, $NaOH/H_2O_2$; [e] **6a**, HBF_4; [f] **6a**, PhSeCl; [g] **6a**, $MeSSMe_2BF_4$; [h] **6a**, H_2CNMe_2I; [i] **6a**, tropylium BF_4; [j] **6a**, 1,3-benzodithiolylium BF_4; [k] **6a**, CF_3I•2DMSO, blue LEDs; [l] **6a**, ICH_2CO_2Et, blue LEDs; [m] **6a**, ICH_2CN, blue LEDs.

The synthetic utility of the three-component coupling process was demonstrated through scaling up the synthesis of **4a** to 3.0 mmol without loss in efficiency (Scheme 4a). Furthermore, high-yielding derivatizations of **4a** provided alcohol **21**, via reductive ozonolysis; and boronic ester **22**, through an enantioselective hydroboration.[22] Finally, BCP-boronic ester **8** was homologated via a lithiation–borylation reaction with enantioenriched carbenoid

23 to give boronic ester **24** in 99% ee (Scheme 4b).[23] The catalyst- and reagent-controlled stereoselective syntheses of chiral BCPs **22** and **24** provide attractive alternatives to current approaches to BCPs with α-stereocenters, which require the use of chiral auxiliaries.[24]



Scheme 4. Synthetic utility of the BCP-derivatives.

In summary, we have developed a synthesis of 1,3-disubstituted BCP derivatives through a three-component coupling reaction of [1.1.1]propellane with organometallic reagents and organoboronic esters. By taking advantage of the versatile C–C bond forming reactions that are possible via 1,2-metallate rearrangements of boronate complexes, this approach could be applied to the synthesis of alkenyl-, alkyl-, and aryl-BCP derivatives. Furthermore, the strategy was extended to a four-component coupling reaction to access tertiary boronic ester-substituted BCPs containing contiguous quaternary centres. This powerful multi-component reaction strategy, with up to three points of diversification, provides a highly modular approach for the preparation of libraries of structurally diverse BCPs.

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Keywords: [1.1.1]Propellane • Bicyclo[1.1.1]pentanes • Multi-Component Reactions • Borylation • Zweifel Olefination

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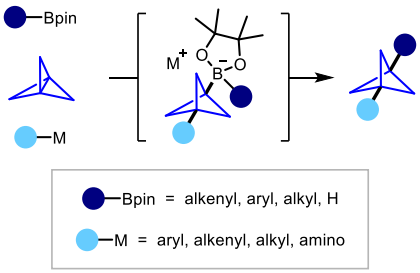
COMMUNICATION

A modular synthesis of 1,3-difunctionalized bicyclo[1.1.1]pentanes has been achieved through multi-component couplings between organometallic reagents, [1.1.1]propellane, and organoboronic esters. By uitilizing the versatile 1,2-metallate rearrangement chemistry of *in situ* generated boronate complexes, a range C–C bond-forming reactions could be carried out without the need for transition metal catalysis.



- *modular synthesis of 1,3-disubstituted BCPs*
- *transition metal-free 3- and 4-component couplings*
- *C–C bond formation via 1,2-rearrangements*

*Songjie Yu, Changcheng Jing, Adam Noble, Varinder K. Aggarwal**

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