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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 sp³-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

[†] These authors contributed equally.

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intermediates 2 are relatively stable to oligomerization with 1 and can be intercepted in palladium- or nickel-catalyzed crosscouplings,^[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 fourcomponent coupling by trapping alkenyl BCP-boronate complexes with a range of electrophiles, enabling rapid access to highly functionalized BCP-derivatives.





b) Stepwise 1,3-difunctionalizations of [1.1.1]propellane



c) Synthesis and reactions of BCP-Grignards generated from [1.1.1]propellane



d) 1,2-Metallate rearragements of BCP-boronate complexes (this work)



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

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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 Zalkenyl 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/alkenylsubstituted 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., nBuLi) 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]

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Table 2. Scope of alkylmetal reagents.



[a] Using 1 (1.2 mmol) and Grignard reagent (0.60 mmol) in Et₂O at 100 °C for 1–2 h, then LiCl (0.60 mmol), **6b** (0.30 mmol), I₂ (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 Et₂O at -78 °C for 30 min, then **6b** (0.45 mmol), I₂ (0.30 mmol) and MeONa (0.90 mmol). [d] Reaction of Bn₂NMgBr-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. HCI, yield in parenthesis is of the corresponding alcohol after in situ oxidation with NaOH/H₂O₂; [b] CICH₂Bpin; [c] furan-2-yl-Bpin, NBS; [d] pyridin-4-yl-Bpin, CICO₂CH₂CCl₃, NaOH/H₂O₂; [e] **6a**, HBF4; [f] **6a**, PhSeCl; [g] **6a**, MeSSMe₂BF4; [h] **6a**, H₂CNMe₂I; [i] **6a**, tropylium BF4; [j] **6a**, 1,3benzodithiolylium BF4; [k] **6a**, CF₃I+2DMSO, blue LEDs; [I] **6a**, ICH₂CO₂Et, blue LEDs; [m] **6a**, ICH₂CN, 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

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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 estersubstituted 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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A modular synthesis of 1,3difunctionalized

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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