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Strain-release 2-azaallyl anion addition/borylation of [1.1.1]propellane: synthesis and functionalization of benzylamine bicyclo[1.1.1]pentyl boronates†
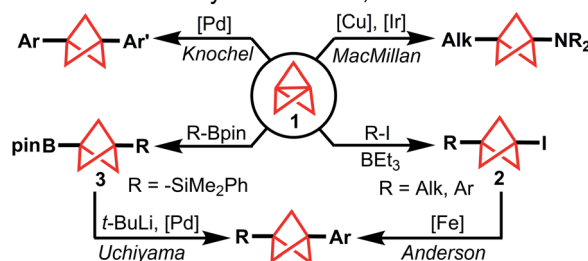
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We report a 3-component reaction between *N*-benzyl ketimines, [1.1.1]propellane, and pinacol boronates to generate benzylamine bicyclo[1.1.1]pentane (BCP) pinacol boronates. These structures are analogous to highly sought diarylmethanamine cores, which are common motifs in bioactive molecules. We demonstrate the versatility of the boronate ester handle *via* downstream functionalization through a variety of reactions, including a challenging Pd-catalyzed (hetero)arylation that exhibits a broad substrate scope. Together, these methods enable the synthesis of high-value BCP benzylamines which are inaccessible by existing methods. Furthermore, we demonstrate the successful application of these newly developed (hetero) arylation conditions to a variety of challenging tertiary pinacol boronates, including nitrogen-containing heterocycles, 1,1-disubstituted cyclopropanes, and other BCP cores.
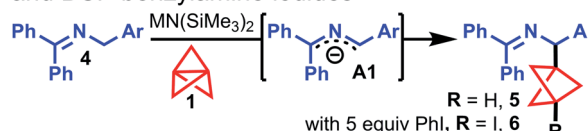
Introduction

Recent years have witnessed significant developments in the synthesis of 1,3-disubstituted bicyclo[1.1.1]pentanes (BCPs).[1,2] Owing largely to an interest from the medicinal chemistry community in the BCP motif as an alkyl bioisostere for aromatic rings in drug-like molecules,[3] synthetic chemists have developed new methods for the direct functionalization of [1.1.1] propellane (**1**). Two common approaches to prepare 1,3-disubstituted BCPs from **1** include: (1) formation of metallated BCP intermediates that can readily form C–C or C–X bonds and (2) synthesis of isolable BCP intermediates that can undergo further structural diversification. For example, Knochel built upon the work of de Meijere and Szeimies[4,5] by generating BCP organomagnesium reagents *via* addition of Grignard reagents to **1**. These intermediates were further transmetallated with ZnCl$_2$ and cross-coupled under palladium catalysis (Scheme 1a, top left).[6] Zinc enolates were also shown to be effective organometallic reagents for addition to **1** followed by electrophile trapping.[7] MacMillan recently demonstrated that BCP radicals (formed from radical addition to **1**) could be intercepted by
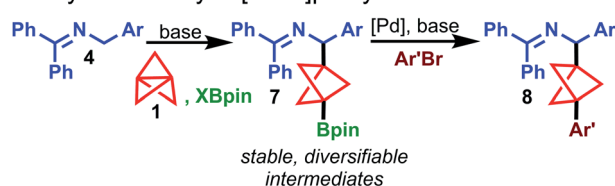

Scheme 1 Select recent syntheses of 1,3-disubstituted BCPs. (a) Knochel, top left: (1) ArMgX, 100 °C then ZnCl$_2$ (2) Ar'X, (dppf)PdCl$_2$, 40–65 °C; MacMillan, top right: (Alk-CO$_2$)$_2$IMes, R$_2$NH, Ir(ppy)$_3$, Cu(acac)$_2$, BTMG, blue LEDs; Anderson, bottom right: Fe(acac)$_3$, TMEDA, ArMgX, 20 °C; Uchiyama, bottom left: *t*-BuLi, −78 °C, then, (dppf)PdCl$_2$, Cu$_2$O, ArBr, 60 °C. (b) Synthesis of BCP benzylamines. (c) This work: synthesis and functionalization of benzylamine bicyclo [1.1.1]pentyl boronates.

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copper-amide species to forge a C–N bond, giving difunctionalized amino BCPs (Scheme 1a, top right).[8]

The synthesis of complex 1,3-disubstituted amino BCPs has been a frequent target of recent work: photochemical,[9] metal-mediated radical chain processes,[10] and "turbo amide"[11] approaches to BCP amine synthesis have been reported. Anderson demonstrated the straightforward synthesis of BCP iodides (2) under Atom Transfer Radical Addition catalysis[12,13] and developed an Fe-catalyzed Kumada coupling with aryl Grignards to access all-carbon 1,3-disubstituted BCP products (Scheme 1a, bottom right).[14] Uchiyama reported the silaboration of 1 to give isolable intermediate 3, which could be subsequently arylated under Pd catalysis (Scheme 1a, bottom left).[15] This work was the first to demonstrate arylation of BCP boronates; however, the arylation protocol requires pre-activation of the boronate with stoichiometric *tert*-butyllithium, which highlights the synthetic difficulty of functionalizing BCP Bpin compounds. Additionally, *t*-BuLi is undesirable from the standpoints of safety, functional group compatibility, and ease of operation. Moreover, general methods for the rapid synthesis of BCP boronates are scarce: Anderson[12] and Aggarwal[16] reported the quenching of BCP organometallics with boronate electrophiles. Decarboxylative borylation of a BCP *N*-hydroxyphthalimide ester furnished the BCP boronate, but this method was not general due to the limited availability of diverse BCP carboxylic acids.[17,18] Thus, general methods to prepare high value BCP boronate intermediates with diverse substitution patterns are still limited.[19]
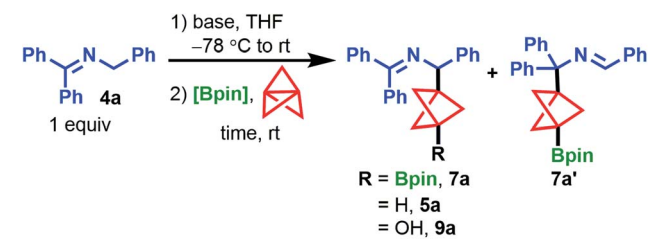
Despite these recent developments, synthetic routes to BCP analogues of many motifs prevalent in drug-like molecules remain elusive. For example, 1,3-difunctionalized BCP analogues of diarylmethanamines, which are privileged structures in medicinal chemistry,[20] are unreported in the current literature and cannot be accessed by the methods described above. To address a synthetic gap in preparing complex BCP diarylmethanamine analogues, we sought to expand our earlier work on the synthesis of BCP benzylamines (5) from *N*-benzyl benzophenone imines (4) and [1.1.1]propellane (1) (Scheme 1b).[21] In this reaction, ketimines 4 are deprotonated under mild conditions to form 2-azaallyl anions A1,[22,23] which are powerful nucleophiles that add to [1.1.1]propellane to give BCP benzylamines 5. During this study, we found the addition of iodobenzene to the reaction mixture enabled iodination of the intermediate BCP anion to give BCP benzylamine iodides (6). The successful capture of this BCP carbanion suggested that a two-electron mechanism was operative for the cleavage of 1 and that capture of this intermediate with other electrophiles might also be possible. Since the functionalization of tertiary iodides generally requires organometallic reagents (*e.g. t*-BuLi, Grignard reagents),[12,14] we explored BCP carbanion capture with other electrophiles with the hope of accessing bench-stable, functionalized BCP benzylamines that could be readily elaborated to more complex substrates. We were particularly attracted to the idea of accessing pinacol boronates, which are both bench-stable and highly versatile synthetic handles.[24,25] Herein, we describe a novel method for the synthesis of 1,3-disubstituted BCP benzylamine pinacol boronates (7) *via*

capture of Bpin electrophiles in the propellylation of 2-azaallyl anions (Scheme 1c). The reaction proceeds with high chemoselectivity to access 1,3-difunctionalized products (7). Additionally, various functional groups on the nucleophilic ketimine are tolerated (*e.g.* –CN, –Br, and –Bpin substituents), which are generally incompatible with difunctionalization methods employing Grignard or organolithium reagents. Furthermore, we present the discovery and development of the first cross-coupling of BCP pinacol boronates with aryl bromides that does not rely on pre-activation of the boronate ester or the use of organometallic reagents. This operationally simple method enables access to complex arylated BCP benzylamines (8) and can be applied to the arylation of other BCP Bpin derivatives as well as select tertiary boronate esters for which no cross-coupling methods are currently known.

Results and discussion

Discovery of the propellylation/borylation reaction began by including 2 equiv. of bis(pinacolato)diboron (B_2pin_2) under our standard propellylation conditions with the 2-azaallyl anion derived from 4a (Table 1, entry 1).[21] By ^{1}H NMR analysis of the crude mixture, we observed the borylated BCP product, 7a, in 43% assay yield (AY, determined by ^{1}H NMR integration against an internal standard) accompanied by 13% AY of protonated product 5a and traces of isomeric product 7a′. Throughout optimization, we aimed to eliminate the formation of 5a, both to improve the product yield and to circumvent difficulty in separating 7a and 5a by column chromatography. Although reducing the equivalents of $LiN(SiMe_3)_2$ from 2.0 to 1.0 improved the yield of 7a, a similar yield of 5a was observed (entry 2). In contrast, switching to $NaN(SiMe_3)_2$ promoted a sluggish reaction (24 h to reach completion) that primarily generated the protonated product, resulting in 25% and 70% AY of 7a and 5a, respectively (entry 3). We hypothesized that 5a arose from reaction of the BCP carbanion with *in situ* generated $HN(SiMe_3)_2$. To eliminate this proton source, we employed 1.1 equiv. of *n*-BuLi as the base which led to the formation of 7a in 49% AY and, as expected, 5a was not detected (entry 4). Switching boron sources from the costly B_2pin_2 to inexpensive *i*PrOBpin (1.1 equiv.) led to a mixture of products, including a 33% AY of 7a and a significant amount of oxidation side product 9a (27% AY) (entry 5), which is presumed to form with traces of oxygen *via* the highly reactive BCP carbanion. Gratifyingly, increasing the equivalents of *i*PrOBpin to five gave 7a in 62% AY, with small amounts of byproducts 5a, 9a, and 7a' detected (entry 6). Cooling the reaction mixture to −78 °C prior to *n*-BuLi addition further improved the AY of 7a to 73% (entry 7). However, while the model reaction using ketimine 4a gave a high AY of product 7a, an initial survey of the reaction scope using these conditions showed poor functional group compatibility with halogenated ketimines due to competing Li–halogen exchange. To mitigate this issue, we replaced *n*-BuLi with lithium diisopropylamide (LDA), which delivered 7a in good yield (74% AY, 61% IY) and improved functional group tolerance during subsequent scope analysis (entry 8). Notably,

Table 1 Optimization of the propellylation/borylation reaction. [1.1.1]propellane (**1**, 1.4 equiv.), reaction concentration = 0.2 M


Entry	Base (equiv.)	Bpin source (equiv.)	Time (h)	% 7a[a]	% 4a[a]	% 5a : 9a : 7a'[a]
1[b]	LiN(SiMe$_3$)$_2$ (2)	B$_2$pin$_2$ (2)	4	43	0	13 : 0 : 5
2[b]	LiN(SiMe$_3$)$_2$ (1)	B$_2$pin$_2$ (2)	7	55	0	18 : 0 : 6
3[b]	NaN(SiMe$_3$)$_2$ (2)	B$_2$pin$_2$ (2)	24	25	0	70 : 0 : 4
4[b,c]	*n*-BuLi (1.1)	B$_2$pin$_2$ (2)	2	49	6	0 : n/d : 4
5[b]	*n*-BuLi (1.1)	*i*PrOBpin (1.1)	2	33	6	10 : 27 : 2
6[b]	*n*-BuLi (1.1)	*i*PrOBpin (5)	2	62	19	5 : 1 : 6
7	*n*-BuLi (1.1)	*i*PrOBpin (5)	2	73	8	0 : 0 : 6
8	**LDA (1.1)**	***i*PrOBpin (5)**	**16**	**74 [61%]**	**14**	**0 : 0 : 7**
9[d]	LDA (1.1)	*i*PrOBpin (5)	2	60	6	0 : 0 : 3

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture using CH$_2$Br$_2$ as an internal standard. [b] Base added at room temperature. [c] ^{1}H NMR spectrum of the crude reaction mixture was too complex to accurately quantify **9a** and **4a**. [d] Reaction initiated at −78 °C and warmed to 50 °C.

heating the reaction mixture to 50 °C for 2 h did not improve the yield of **7a** further (60% AY, entry 9).

With optimized conditions in hand, we surveyed the scope of the propellylation/borylation reaction with ketimines **4** and aldimines **4′** (Scheme 2). Electron-withdrawing groups were best

Scheme 2 Scope of the propellylation/borylation reaction. All products were generated from ketimines **4** except for **7h** and **7o**, which were generated from aldimines **4h′** and **4o′**, respectively, due to ease of synthetic access. [a] 60 °C, 16 h.

tolerated in this transformation, producing high yields of products **7**. Imine starting materials possessing trifluoromethoxy, chloro and bromo groups were well-tolerated, affording the products **7b–e** in 57–70% yield. Substrates bearing 3-methoxy and 4-cyano substituents were also viable, generating products **7f** and **7g** in 52% and 40% yield, respectively. In these two cases, as well as other lower yielding reactions, no other major BCP-related products were detected even though the reactions reached >90% conversion. Therefore, we attribute these low yields to decomposition of the 2-azaallyl anion intermediates under the reaction conditions. Aldimine **4h′**, bearing an aryl boronic ester, underwent the reaction in 39% yield to produce **7h**, which possesses two Bpin handles that can be further derivatized *via* orthogonal functionalization.[26,27] Ketimines substituted with electron-donating *tert*-butyl and methoxy groups were also successful in the reaction but produced higher proportions of isomeric products **7j′** and **7k′** (**7j** and **7k**, 35% and 49%, respectively). Notably, we observed significant amounts of the isomeric products in our study of 2-azaallyl anion propellylation/protonation when ketimines bearing electron-donating groups were used.[21] Despite the sterically hindered nature of *ortho*-methyl substituted imine **4l**, the desired product was obtained in good yield, affording a mixture of **7l** and **7l′** in 63% and 7% yields, respectively. Importantly, several pharmaceutically relevant heterocycle-derived ketimines also provided products in synthetically useful yields. 3-Pyridyl-substituted **7m** was generated in 41% yield after heating at 60 °C for 16 h and morpholine-substituted pyridine product **7n** could be formed in 39% yield. Moreover, a pyrrole and benzothiophene group could also be smoothly incorporated into products **7o** and **7p**, respectively. Finally, while most of these experiments were conducted on 0.2 mmol scale, the reaction could be easily scaled-up without any
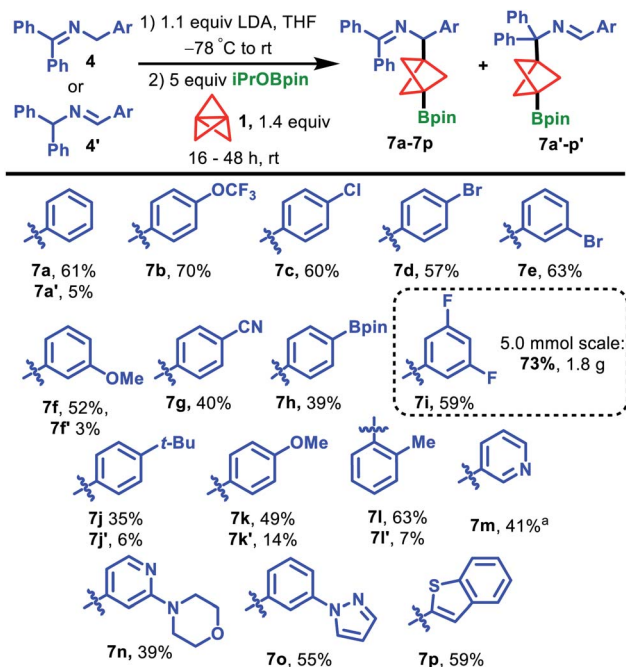
detrimental impact on the yield. For instance, a 5.0 mmol scale reaction of ketimine **4i** produced 1.8 g (73% yield) of the corresponding BCP Bpin product **7i**. We note that, despite the indefinite shelf-stability of BCP BPin products **7** to air and moisture, the high sensitivity of these compounds towards silica and alumina necessitates their purification on C_{18}-end-capped reversed-phase silica gel.

To demonstrate the utility of these borylated products, we turned our attention to functionalization of the tertiary Bpin group, using **7b** and **7i** as model substrates (Scheme 3). C–N bond formation using DIAD furnished hydrazine dicarboxylate **10** in 24% yield (top).[28] Aggarwal's conditions for oxidative arylation with electron-rich arenes were also tolerated, producing furylated product **11** in 66% yield from **7i** (top right). To further demonstrate the compatibility of substrates **7** with certain organometallic reagents, **7i** was subjected to Zweifel olefination conditions, giving the vinylated product **12** in 44% yield (bottom right).[29] A recent modification on the Barluenga–Valdés reaction, which couples alkylboronic acids with sulfonylhydrazones,[30] was successful with the boronic acid of **7i** and sulfonylhydrazone **13** to produce **14** in 55% yield (bottom). Furthermore, oxidation of **7i** to alcohol **15** proceeded smoothly in 78% yield (bottom left).

To further explore the utility of these BCP Bpin products, we were interested in examining their cross-coupling with aryl halide partners. Following the state-of-the-art in BCP Suzuki cross-coupling, we attempted Uchiyama's arylation of BCP Bpin derivatives *via* sequential *t*-BuLi activation and Pd catalysis (Scheme 3, top left).[15] We found that subjecting **7b** to these

Scheme 3 Functionalization of the benzylamine BCP Bpin. [a] (i) 1.2 equiv. 4-lithioanisole, THF, −78 °C, 30 m, then rt, 30 m. (ii) 2.5 equiv. diisopropyl azodicarboxylate (DIAD), rt, 16 h. [b] **7i** used as 2.2 equiv. relative to limiting reagent, tosylsulfonylhydrazone. (i) 2.2 equiv. $NaIO_4$, THF/H_2O, 1 h, then sat'd aq. NH_4Cl, 24 h; 1 equiv. **13**, 1.5 equiv. Cs_2CO_3, 1,4-dioxane, 110 °C, 18 h.
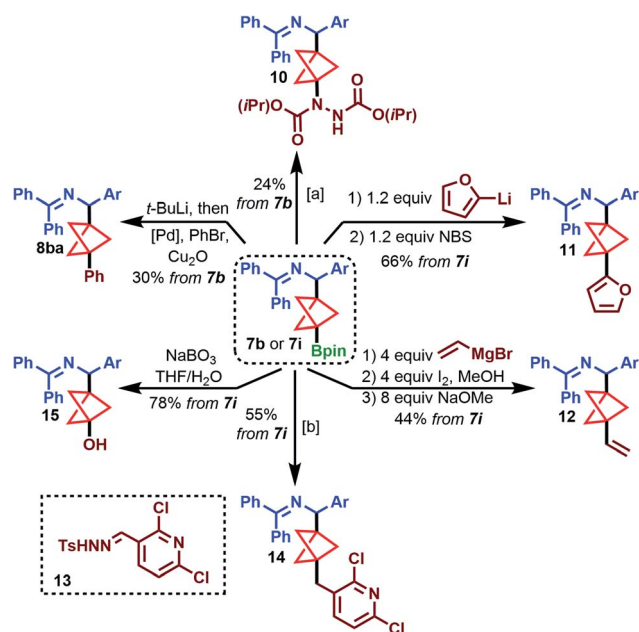
literature conditions gave 30% yield of the bromobenzene-derived arylated product **8ba**. This result might reflect some level of incompatibility of benzylamine BCP pinacol boronates with *t*-BuLi, most likely due to competitive attack of the highly reactive organolithium reagent at the boron center and at the acidic benzylic proton of the ketimine. Moreover, *t*-BuLi is expected to be incompatible with halogenated substrates such as **7c** and **7d** due to competitive metal–halogen exchange. Thus, we sought to develop a more general BCP Bpin arylation protocol that did not require pre-activation of the Bpin ester.[15]

We initially utilized high-throughput experimentation (HTE) to broadly survey potentially viable catalysts and solvents for the arylation of ketimine BCP Bpin **7a** with PhBr (Table 2). A screen of six phosphine ligands [cataCXium A (*n*-BuP(1-Ad)$_2$), P(*t*-Bu)$_3$, DTBPF, RuPhos, XPhos, and sSPhos] and 4 solvents (PhMe, CPME, *t*-AmOH, and DMF; 0.1 M) in the presence of aq. Cs_2CO_3 (3 equiv.) at 100 °C revealed cataCXium A and P(*t*-Bu)$_3$ to be the most effective ligands for arylation of **7a** (2.5 μmol scale; see ESI, S33–S37†). Unfortunately, bench-scale evaluation of the best result (cataCXium A in PhMe, 0.05 mmol scale) showed only 5% AY of the arylation product **8aa** with 71% AY of **7a** remaining (Table 1, entry 1). Increasing the reaction temperature to 120 °C under otherwise identical conditions improved the AY to 21%, leading us to continue our optimization efforts at this temperature (entry 2). Extensive screening of potential ligands, bases, and solvents at 120 °C confirmed cataCXium A as the top performing ligand and showed CPME/aq. Cs_2CO_3 to be the most effective solvent/base combination.

To avoid complications in reaction analysis (with C3 isomer **7a'** being present in our starting material), we opted to utilize substrate **7i** during our continued optimization. Under these conditions, arylation of **7i** with PhBr gave a promising 43% AY of **8ia**, albeit with significant quantities of **7i** remaining (entry 3). We found that increasing the reaction concentration 4× (to 0.4 M) improved the yield to 55% (entry 4). During our optimization, we identified an *N*-arylated carbazole side product, which formed from the Pd precatalyst and co-eluted with **8ia** during chromatographic separation. By replacing the precatalyst with Pd(OAc)$_2$ and cataCXium A in a 1 : 2 ratio, we effectively eliminated its presence and improved the AY to 62%. It is worth noting that at this stage we opted to complete our optimization of this arylation reaction on substrate **7b** rather than **7i**, due to the latter's propensity to undergo C–H arylation between the fluoro groups on the 3,5-F$_2$-C$_6$H$_3$ ring when certain aryl bromides were used.

Copper(I) oxide (Cu$_2$O) has recently been reported to facilitate arylation of sterically encumbered nucleophiles[15,31] and we hypothesized that this additive could also prove beneficial for our coupling. Gratifyingly, we found that the addition of 1 equiv. Cu$_2$O further improved the yield to 69% AY (53% IY of **8ba**, entry 6). Employing 2 equiv. of Cu$_2$O was found to slightly diminish the yield to 56% AY (entry 7).

Having optimized the conditions for the challenging arylation of our BCP Bpin building blocks, we probed the scope of this transformation using substrate **7b**. We first examined electron-neutral aryl bromides in the coupling reaction (Scheme 4). 2-Naphthyl and 3-benzocyclobutyl groups were tolerated in

Table 2 Optimization of the BCP Bpin cross-coupling reaction

Entry	BCP Bpin	Catalyst[a]	Solv., add.	% 8[b]	% 7 remaining[b]
1[c]	**7a**	cataCXium A G2	PhMe (0.1 M)	5	71
2	**7a**	cataCXium A G2	PhMe (0.1 M)	21	55
3	**7i**	cataCXium A G2	CPME (0.1 M)	43	46
4	**7i**	cataCXium A G2	CPME (0.4 M)	55	25
5	**7i**	Pd(OAc)$_2$/cataCXium A (1 : 2)	CPME (0.4 M)	62	9
6	**7b**	**Pd(OAc)$_2$/cataCXium A (1 : 2)**	**CPME (0.4 M), Cu$_2$O (1.0 equiv.)**	**69 (53% IY)**	**18**
7	**7b**	Pd(OAc)$_2$/cataCXium A (1 : 2)	CPME (0.4 M), Cu$_2$O (2.0 equiv.)	56	8

[a] CataCXium A: (n-Bu)P(1-Ad)$_2$, di(1-adamantyl)-n-butylphosphine. [b] AY as determined by ^{1}H NMR analysis of the crude reaction mixture against CH$_2$Br$_2$ as an internal standard. [c] Reaction performed at 100 °C, 0.1 M.
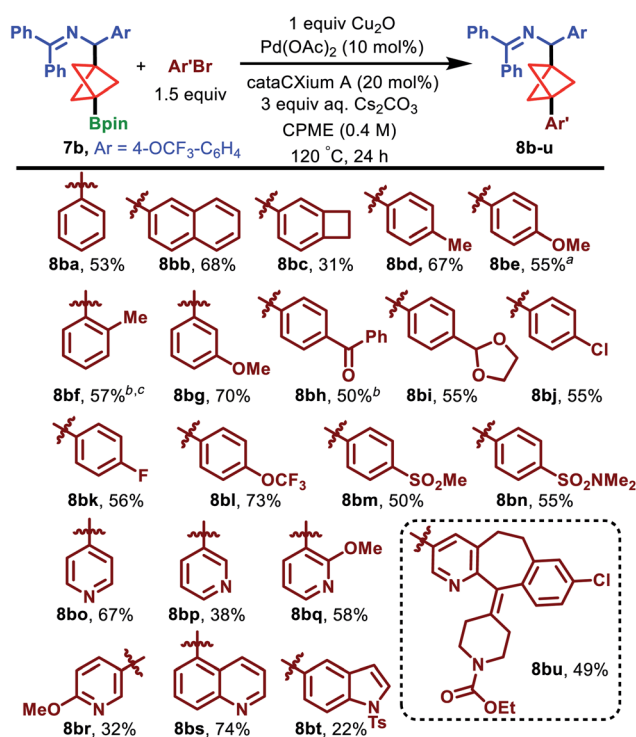
Scheme 4 Scope of the cross-coupling reaction. [a]Microwave irradiation conditions, 100 °C, 24 h, using **7b** and 4-bromoanisole, gave 73% AY, compared to 77% AY for standard conditions (as shown, heating in an oil bath). [b]No Cu$_2$O additive. [c]n-Bu$_2$O solvent, 140 °C.

the reaction, producing **8bb** and **8bc** in 68% and 31% yield, respectively. The low yield of **8bc** is attributed to a high proportion of unreacted starting material (32% AY) as well as significant quantities of homocoupled aryl bromide (Ar′–Ar′), as determined by ^{1}H NMR analysis of the crude mixture.

Electron-rich substrates 4-bromotoluene and 4-bromoanisole delivered arylation products **8bd** and **8be** in 67% and 55% yield, respectively. Notably, 2-bromotoluene was successfully coupled upon heating to 140 °C in n-Bu$_2$O and in the absence of Cu$_2$O, producing the highly encumbered **8bf** in 57% yield.

We next turned to electron-poor aryl bromides. 3-Bromoanisole and 4-bromoacetophenone furnished the arylation products **8bg** and **8bh** in 70% and 50% yield, respectively. Interestingly, the latter substrate performed more effectively in the absence of Cu$_2$O. Moreover, para-1,3-dioxolo-, halo-, trifluoromethoxy-, and sulfonyl-derived aryl bromides each performed well and formed products **8bi–8bn** in 50–73% yield.

Heterocyclic aryl bromides are absent in the existing BCP Bpin cross-coupling literature and, given their importance in medicinal chemistry, we were pleased to observe the coupling of 4- and 3-bromopyridine to deliver **8bo** and **8bp**, respectively, in synthetically useful yields of 67% and 38%.[32] Substitution of the pyridine was also tolerated, as demonstrated by the formation of methoxy-substituted pyridines **8bq** and **8br** in 58% and 32% yield, respectively. Moreover, both quinoline (**8bs**, 74%) and indole (**8bt**, 22%) substrates could be coupled under the standard conditions. We observed a 49% yield of **8bu** when a loratadine-derived aryl bromide was employed in the reaction, further demonstrating the compatibility of hydrolytically sensitive functional groups, nitrogen heterocycles, and aryl chlorides under these conditions. Lastly, we established that the arylation is also effective at slightly lower temperatures when conducted under microwave irradiation. Specifically, compound **8be** was produced in 73% AY after 24 h at 100 °C under microwave irradiation (cf. 77% AY, 55% IY under the standard conditions at 120 °C in an oil bath).

Importantly, the imine products can be readily hydrolyzed to the corresponding free amine, as exemplified by the conversion of **8bo** to **16** in 87% yield (Scheme 5). This demonstrates the ease in which complex, high-value arylated BCP benzylamines can be accessed using these new methods.

Though our arylation conditions had been optimized for benzylamine BCP Bpin substrates (7), they could also be applied to the coupling of other tertiary pinacolboronates. The coupling
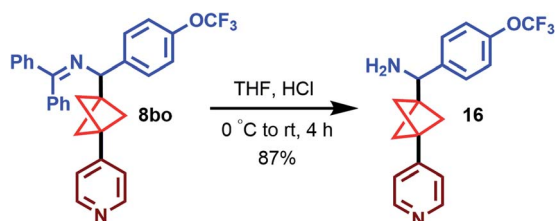
Scheme 5 Hydrolysis of the arylation product.

of tertiary C(sp³) centers and arenes is an important area of research, with several advances being reported recently. Tertiary redox-active esters have been coupled with aryl Grignard and arylzinc reagents.[33] Boracene-based alkylborates facilitate coupling of tertiary radicals derived from alkyllithiums under Ni catalysis.[34] Zn/Ni-mediated catalysis has also been effective for the coupling of tertiary bromides and tertiary oxalates with aryl and acrylate-based electrophiles.[35,36] Boron-based reagents that do not require pre-activation (*e.g. t*-BuLi activation or coordination of an alkyllithium to an arylboron-based reagent to form a photoexcitable complex), namely tertiary potassium trifluoroborates, undergo arylation in both photoredox and Pd-catalyzed contexts.[37–39] We suspected that successful coupling of tertiary Bpin reagents, which are invariably the precursor to tertiary trifluoroborate salts, would enable more rapid assembly of highly desirable C(sp³)-rich scaffolds.[40] Facile arylation of tertiary Bpins would also present an attractive synthetic option that precludes the use of added organometallic reagents and/or undesired synthetic manipulations.

To probe the generality of our cross-coupling conditions on non-BCP substrates, we examined the arylation of several commercially available tertiary pinacol boronates **17a–f** with 4-bromo-*N,N*-dimethylbenzenesulfonamide (Scheme 6). We were pleased to find that 3-azabicyclo[4.1.0]heptanes **17a** and **17b** coupled in excellent yields of 95% and 82%, respectively, saving a synthetic step from the previously reported coupling of their BF₃K derivatives.[39] Methylcyclopropane **17c** coupled in 70% yield by inverting the ratio of Bpin and aryl bromide,

which helped facilitate purification of the product. Notably, coupling of the methylcyclopropane fragment with aryl halides is virtually unreported in the present literature, with a single example producing arylated product in 6% yield.[41] We next examined 1-phenylcyclopropane **17d**. The BF₃K analogue of this substrate was shown previously to couple using cata-CXium A G2 precatalyst, Cs₂CO₃ in PhMe/H₂O at 95 °C,[39] conditions which returned only starting materials when applied to the coupling of the Bpin substrate **17d**. Under our coupling conditions, a 59% yield of 1,1-diarylcyclopropane product **18d** from the pinacol boronate was obtained. Efficient coupling of trifluoromethyl-substituted BCP **17e** is an unsolved challenge in the current synthetic literature. In a recent report, it could only be converted to the corresponding BF₃K in 4.5% yield,[17] highlighting the potential utility of a coupling method which obviates the need for BF₃K formation. Gratifyingly, under our standard conditions, we observed a 54% yield of the desired arylation product **18e** (Scheme 6, bottom left). We also studied the arylation of Uchiyama's silaborated BCP,[15] **17f**, under our conditions. Using 1-bromo-4-(trifluoromethoxy)benzene, which was successful in Uchiyama's study to produce **18f**, we obtained a 10% improvement in isolated yield (65%). This demonstrates similar efficacy of our reaction conditions *versus* the current state-of-the-art, but without the need for *t*-BuLi pre-activation.
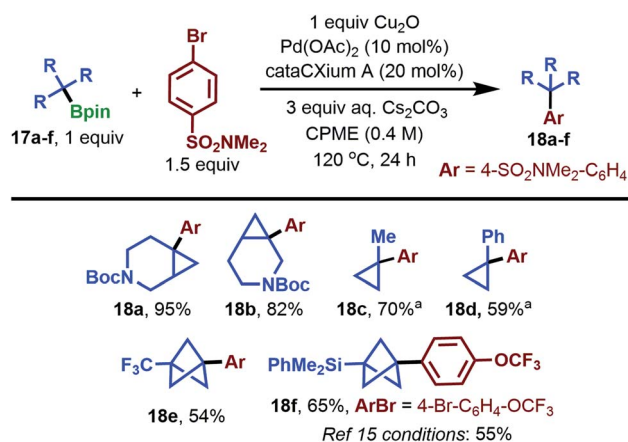
Conclusions

In summary, we have developed a 2-azaallyl anion addition/borylation reaction of [1.1.1]propellane to prepare new 1,3-difunctionalized benzylamine BCP pinacol boronates of structural relevance to a number of bioactive scaffolds. Functionalization of the boronate ester *via* oxidation, C–N, and C–C bond formation were shown to be effective. Further, we addressed a gap in the BCP cross-coupling literature by developing an arylation of BCP Bpin derivatives under Pd catalysis that does not require pre-activation of the boronate ester or the use of added organometallic reagents. These conditions enable facile arylation of benzylamine BCP Bpin compounds with a broad range of aryl bromides and were also readily applied to other tertiary Bpin-containing structures, including those possessing nitrogen heterocycles, cyclopropanes, and BCPs for which arylation has not yet been demonstrated. This underscores the broad utility of this method to enable the synthesis of C(sp³)-rich scaffolds in a variety of contexts.

Scheme 6 Tertiary pinacol boronate scope in the cross-coupling reaction. ª Ratio of Bpin to ArBr is 1.5 : 1.

Author contributions

The work was conceptualized by RAS, JMEH, RRM and PJW. Experiments were performed by RAS, AC, YP and JMEH. The first draft of the manuscript was prepared by RAS and the final draft was edited by all the authors.

Conflicts of interest

There are no conflicts to declare.

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