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Accessing 2-(Hetero)arylmethyl-, -allyl-, and -propargyl-2,1-borazaronaphthalenes: Palladium-Catalyzed Cross-Couplings of 2-(Chloromethyl)-2,1-borazaronaphthalenes

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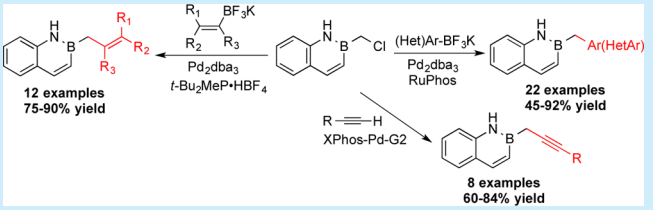
Supporting Information

ABSTRACT: The synthesis of 2-(chloromethyl)-2,1-borazaronaphthalene has provided an opportunity to expand dramatically the functionalization of the azaborines. This azaborinyl building block can serve as the electrophile in palladium-catalyzed cross-coupling reactions to form sp^3–sp and sp^3–sp^2 bonds. The cross-coupling reactions of 2-(chloromethyl)-2,1-borazaronaphthalene with potassium (hetero)aryl- and alkenyltrifluoroborates as well as terminal alkynes provides access to a variety of novel azaborines, allowing a library of pseudobenzylic substituted azaborines to be prepared from one common starting material.

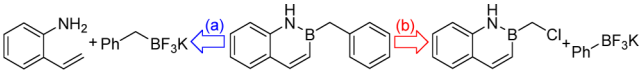


The ability of benzylic halides to serve as electrophiles in substitution reactions is one of the principal reasons for the exceptional utility of this class of molecules as important synthetic intermediates.[1a,b] Recently, we developed the synthesis of 2-(chloromethyl)-2,1-borazaronaphthalene, a pseudobenzylic halide azaborine analogue, and have demonstrated its ability to serve as an electrophile in substitution reactions, affording B–N isosteres of benzylic amines, ethers, thioethers, and esters.[2] However, the importance of benzylic halides extends beyond their ability to serve as electrophiles in substitution reactions because these reagents can also serve as electrophiles in metal-catalyzed coupling reactions.[3] The products of these cross-coupling reactions have applications in many areas of chemistry, including medicinal chemistry, agrochemistry, and materials science.[4]

Specifically, even though diarylmethanes are important synthetic products, these molecules are not ideal drug candidates because they are prone to benzylic oxidation.[5] Recently, Liu, Heider, et al. reported that the B–N isosteres of ethylbenzene inhibit the ethylbenzene dehydrogenase (EbDH) enzyme, possibly because of the higher energy of activation required to oxidize the pseudobenzylic position relative to that of ethylbenzene.[6] On the basis of this precedent, the synthesis of B–N-diarylmethane azaborines could provide a pathway to the utilization of diarylmethane derivatives in medicinal chemistry.

The two main retrosynthetic disconnections to synthesize 2-(hetero)arylmethyl-2,1-borazaronaphthalenes are shown in Scheme 1. The first route (a) is the annulation of 2-aminostyrene and potassium benzyltrifluoroborate. This route has been developed as an efficient way to access 2,1-borazaronaphthalenes.[7] Although this route can be employed, the synthesis of a library of azaborines would require a wide variety of benzylic trifluoroborates, many of which are not commercially available and would therefore need to be prepared individually. Another disconnection (b) is the metal-catalyzed cross-coupling of 2-(chloromethyl)-2,1-borazaronaphthalene with a (hetero)-aryltrifluoroborate, wherein a library of derivatives could be prepared from the vast number of commercially available organotrifluoroborates. Because the stability of 2-(chloromethyl)-2,1-borazaronaphthalene to copper-catalyzed reactions (e.g., azide–alkyne Huisgen cycloaddition) has been recently reported,[2] this route would appear to provide access to an array of 2-benzyl-2,1-borazaronaphthalenes via the Suzuki–Miyaura cross-coupling reaction.

Scheme 1. Two Retrosynthetic Disconnections To Synthesize 2-Benzyl-2,1-borazaronaphthalene



The Suzuki–Miyaura cross-coupling reaction is one of the most important C–C bond-forming reactions because it employs organoboron reagents that are bench stable and exhibit minimal toxicity. Additionally, the mild reaction conditions lead to higher functional group tolerability.[8] Of the possible organoboron derivatives, potassium organotrifluoroborates can be advantageous because of their enhanced air and moisture stability, which allows a near stoichiometric amount to be employed relative to the electrophile.

Using 2-(chloromethyl)-2,1-borazaronaphthalene, **1**, and potassium phenyltrifluoroborate as model coupling partners, an extensive screening of various reaction parameters (e.g., solvent, palladium catalyst, ligand, base, temperatures) was

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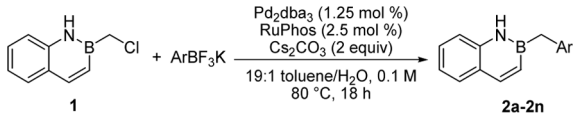
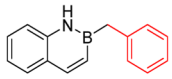
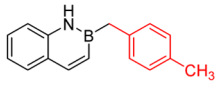
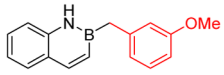
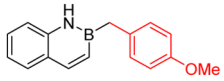
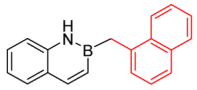
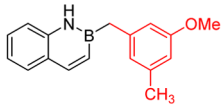
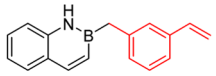
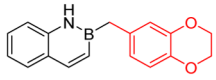
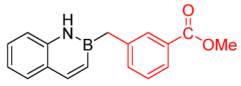
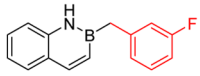
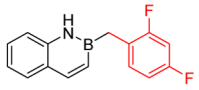
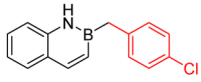
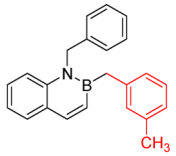
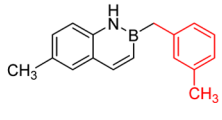
carried out.[9] These studies revealed that the combination of 1.25 mol % of Pd_2dba_3, 2.5 mol % of RuPhos, and Cs_2CO_3 in a toluene/H_2O solvent system provided the desired product in 90% yield (Table 1, entry 1). The optimal reaction conditions were applied to the cross-coupling reaction of **1** with an array of both electron-rich (entries 1–8) and electron-poor (entries 9–12) aryltrifluoroborates. All of the aryltrifluoroborates utilized were successfully cross-coupled in yields of 45–92%. To demonstrate that these reaction conditions can be extended to the cross-coupling of substituted 2-(chloromethyl)-2,1-borazaronaphthalenes, the cross-coupling reaction of *N*-benzyl-2-(chloromethyl)-2,1-borazaronaphthalene and 6-methyl-2-(chloromethyl)-2,1-borazaronaphthalene with potassium 3-methylphenyltrifluoroborate as the nucleophilic partner were completed. The corresponding products were isolated in yields of 79% and 83%, respectively (Table 1, entries 13 and 14). The scalable nature of the coupling was illustrated by performing the reaction on a 5 mmol scale, with 1.2 mol % of Pd_2dba_3, providing product **2a** in 88% yield (Table 1, entry 1).

To extend the scope of the method, the general reaction conditions were then applied to a variety of potassium heteroaryltrifluoroborates (Table 2). Accordingly, 2-(chloromethyl)-2,1-borazaronaphthalene was efficiently coupled with a variety of nitrogen-, oxygen-, and sulfur-containing heteroaryltrifluoroborates in yields up to 90%. As with the aryltrifluoroborates, substitution of the 2-(chloromethyl)-2,1-borazaronaphthalene core does not interfere with the coupling, and the desired products were isolated in good yields (Table 2, entries 6–8).

The success of the cross-coupling with (hetero)aryltrifluoroborates encouraged an investigation of the cross-coupling of 2-

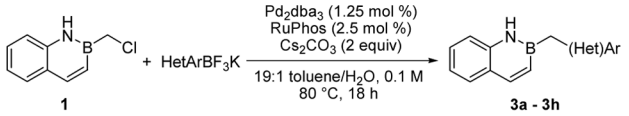
Table 1. Scope of the Cross-Coupling with Potassium Aryltrifluoroborates

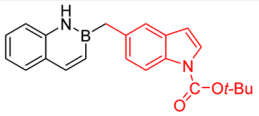
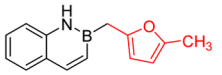
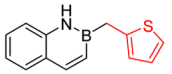
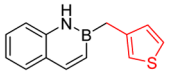
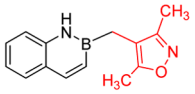
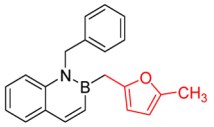
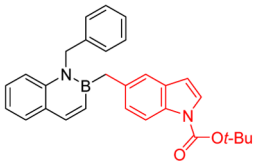
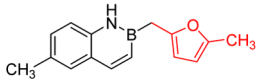


entry	product		% yield
1		2a	90 (88)[a]
2		2b	92
3		2c	85
4		2d	89
5		2e	91
6		2f	92
7		2g	80
8		2h	82
9		2i	58
10		2j	61
11		2k	59
12		2l	45
13		2m	79
14		2n	83

[a]Reaction completed on a 5 mmol scale.

Table 2. Scope of the Cross-Coupling with Potassium Heteroaryltrifluoroborates



entry	product		% yield
1		3a	90
2		3b	67
3		3c	46
4		3d	70
5		3e	80
6		3f	70
7		3g	84
8		3h	78

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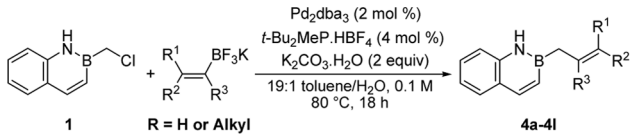
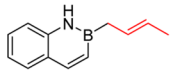
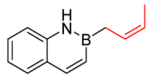
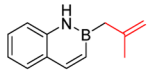
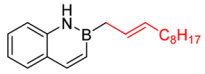
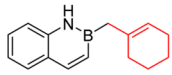
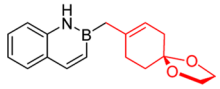
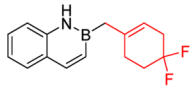
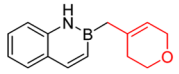
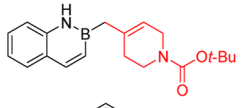
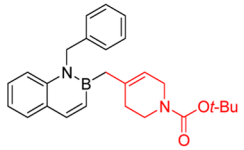
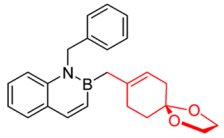
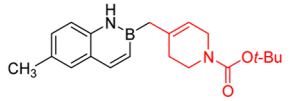
(chloromethyl)-2,1-borazaronaphthalene with other nucleophiles. The cross-coupling of 2-(chloromethyl)-2,1-borazaronaphthalene with potassium alkenyltrifluoroborates would afford a family of *B*-allyl-substituted azaborines. Initial efforts focused on optimizing conditions under which **1** coupled to potassium *trans*-1-propenyltrifluoroborate (Table 3, entry 1). Using microscale high-throughput experimentation (HTE), an array of palladium catalysts, ligands, bases, and solvents was examined.[9] Extensive screening revealed that a combination of Pd_2dba_3, *t*-$Bu_2MeP{\cdot}HBF_4$, and K_2CO_3 in a toluene/H_2O solvent system at 80 °C afforded the desired cross-coupled product in 90% isolated yield.

Table 3. Scope of the Cross-Coupling with Potassium Alkenyltrifluoroborates



entry	product		% yield
1		4a	90 (91)[a]
2		4b	82
3		4c	80
4		4d	89
5		4e	86
6		4f	84
7		4g	75
8		4h	79
9		4i	83
10		4j	80
11		4k	90
12		4l	78

[a]Reaction completed on a 5 mmol scale.

The scope of this method was investigated by extending the cross-coupling to a variety of alkenyltrifluoroborates (Table 3). The coupling of potassium *cis*-1-propenyltrifluoroborate produced the desired product in 82% yield. Importantly, complete retention of configuration was observed in this cross-coupling (entry 2). Cyclic alkenyltrifluoroborates bearing a variety of functional groups proved effective in the reaction (entries 6−12), and the scalable nature of the cross-coupling was again illustrated by treating 5 mmol of **1** with *trans*-1-propenyltrifluoroborate using 2 mol % of Pd_2dba_3, providing product **4a** in 91% yield (Table 1, entry 1). 2-(Chloromethyl)-2,1-borazaronaphthalenes substituted at various positions served as electrophiles in this reaction, providing the corresponding cross coupled products in high yields (entries 10−12).

Lastly, an investigation was undertaken to determine whether Sonogashira coupling reactions could be effected on the 2-(chloromethyl)borazine derivatives. Although significant advances in metal-based systems to catalyze the reaction of aryl halides and terminal alkynes have been made, reports for the coupling of alkyl or benzyl halides are rare. Generally, methods to install alkynyl groups involve the use of alkynylmetallics such as alkynylzinc reagents,[10] tris(alkynyl)indiums,[11] or a palladium/copper co-catalyst in conjunction with terminal alkynes.[12] Another challenging feature of this transformation is that the Sonogashira reaction of benzyl halides often results in the formation of substituted enynes through a Sonogashira−carbopalladation−Sonogashira sequence.[13]

Extensive screening revealed that the cross coupling of **1** with phenylacetylene as a model alkyne in the presence of 2 mol % of XPhos-Pd-G2 and 1.05 equiv of Cs_2CO_3 as a base in a toluene/H_2O solvent mixture produced the desired cross-coupling product in 84% yield (Table 4, entry 1).[9] An array of terminal alkynes were subjected to the standard reaction conditions, affording the desired products in good yield. Terminal arylalkynes containing electron-donating and electron-withdrawing substituents (entries 2−4) were successfully coupled, affording the desired products in yields up to 84%. Terminal aliphatic alkynes incorporating cyclohexenyl and cyclopropyl subunits were effective, providing the corresponding products with 74% and 60% yields, respectively (entries 5 and 6). The general reaction conditions were further extended to substituted azaborines, demonstrating that substitution on the azaborine substructure does not interfere with the coupling (entries 7 and 8). The scalable nature of this coupling was demonstrated by performing the reaction on a 5 mmol scale, using 2 mol % of the palladium catalyst, providing the corresponding product in 80% yield (entry 1).

The importance of the metal-catalyzed transformations developed herein becomes evident when compared to syntheses of isosteric 2-(chloromethyl)naphthalenes. To the best of our knowledge,[14] there is only one example of a cross-coupling to install an arene in the latter, and this involves a Hiyama coupling.[15] Further, the addition of $AlMe_3$ across an alkyne followed by transmetalation to a zirconium species is the only alkenyl nucleophile reported for a coupling with 2-(chloromethyl)naphthalene.[16] Generalizing this route would appear to suffer from a limited substrate scope because it employs a rather harsh Lewis acid. The reaction between 2-(chloromethyl)naphthalene and a terminal alkyne proceeds in the presence of CuI but requires 36 h.[17] The method developed herein affords a wide variety of alkynyl substituents in one step.

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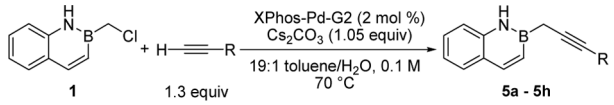
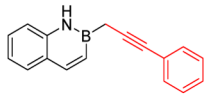
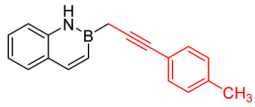
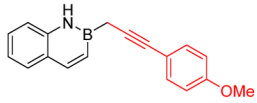
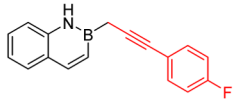
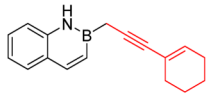
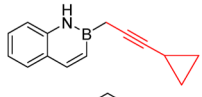
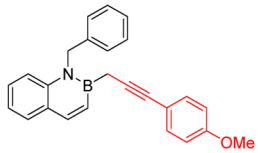
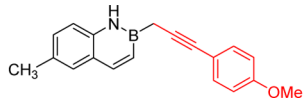
Table 4. Scope of the Cross-Coupling with Terminal Alkynes



entry	product		% yield
1		5a	84 (80)[a]
2		5b	79
3		5c	81
4		5d	70
5		5e	74
6		5f	60
7		5g	78
8		5h	80

[a]Reaction completed on a 5 mmol scale.

Lastly, and perhaps most importantly, the synthesis of the all-carbon isosteric naphthalenes with further substitution about the naphthalene ring would be much more difficult than that demonstrated herein in the azaborine system. The ability to synthesize a substituted 2,1-borazaronaphthalene with complete regiochemical control, and then employ that intermediate as an electrophile in a cross-coupling, allows rapid elaboration of the 2,1-borazaronaphthalenes in two short steps.

In conclusion, the electrophilic nature of 2-(chloromethyl)-2,1-borazaronaphthalene has been expanded from substitution reactions to include several metal-catalyzed reactions. Potassium (hetero)aryl- and alkenyltrifluoroborates as well as terminal alkynes are successful nucleophiles, affording a wide variety of substituted azaborines from one common azaborinyl building block.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, HTE data, compound characterization data, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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