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Accessing an Azaborine Building Block: Synthesis and Substitution Reactions of 2-Chloromethyl-2,1-borazaronaphthalene

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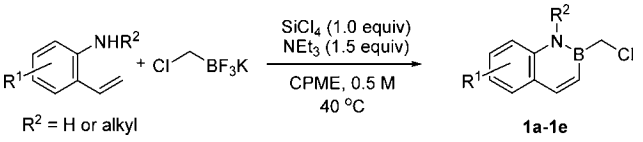
Supporting Information

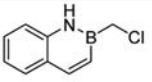
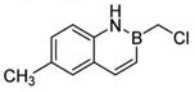
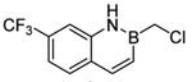
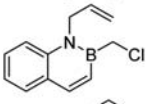
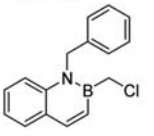
ABSTRACT: One major synthetic route to the synthesis of benzyl amines, ethers, and esters is the nucleophilic substitution of a benzylic halide. To develop a method for the facile synthesis and functionalization of the isosteric azaborines, 2-chloromethyl-2,1-borazaronaphthalene has been synthesized in one step to afford a similar common precursor to a benzylic halide. This B−N isostere has been shown to be an effective building block by serving as an electrophile in substitution reactions with a large variety of nucleophiles.

Benzylic halides are important synthetic intermediates because they provide access to a wide array of compounds with applications in medicinal chemistry, agrochemistry, and materials science.[1a−g] Similarly, azaborines have been investigated for related applications.[2a−c] Because the B−N bond is isoelectronic and isosteric with the C=C bond, medicinal chemists have explored B−N/C=C isosterism to increase structural variety and access new bioactive compounds that show antibacterial and antifungal activities.[3a−d] Consequently, the development of a method for the functionalization of azaborines could have a great impact on the discovery of novel drug candidates. However, until recently, research on azaborines has been focused on their core, with further functionalization of an azaborine limited to boron and simple electrophilic aromatic substitution of the azaborine substructure.[4a,b] Through efforts to expand the chemistry of 2,1-borazaronaphthalenes as a means to demonstrate its utility as a C−C analog of naphthalene, a method has been developed to synthesize this core starting from potassium organotrifluoroborates.[5] Over 480 potassium organotrifluoroborates are commercially available, so the opportunities to synthesize a wide array of functionalized 2,1-borazaronaphthalenes are vast. As one exemplar, we sought to exploit this method to synthesize pseudobenzylic halides of 2,1-borazaronaphthalenes, where the pseudobenzylic halide can serve as a handle for further functionalization, providing access to more highly elaborated azaborines building blocks.

Utilizing the previously developed conditions for the preparation of 2,1-borazaronaphthalenes,[5] the annulation of potassium chloromethyltrifluoroborate and 2-aminostyrene to yield the desired 2-chloromethyl-2,1-borazaronaphthalene **1a** resulted in a low yield of the desired product. Upon switching the solvent from a toluene/cyclopentyl methyl ether (CPME) to CPME, side product formation decreased such that 2-chloromethyl-2,1-borazaronaphthalene was afforded in 71% yield (Table 1, entry 1). The optimal solution concentration was found to be 0.5 M. Lower concentrations caused lower yields,

Table 1. Scope of the Synthesis of 2-Chloromethyl-2,1-borazaronaphthalenes



entry	product		% yield
1		**1a**	71
2		**1b**	88
3		**1c**	58
4		**1d**	66
5		**1e**	77

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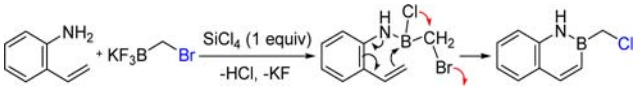
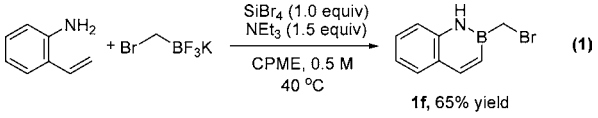
and higher concentrations resulted in a thick slurry that was unable to be stirred efficiently. Several different substituted 2-chloromethyl-2,1-borazaronaphthalenes can be prepared under these modified conditions (Table 1). Substitution of the all-carbon ring with electron-donating and electron-withdrawing groups is permitted, providing the corresponding azaborine in yields up to 88% (entries 2−3). Further, substitution on nitrogen does not affect the annulation, and *N*-substituted azaborines can be obtained in good yields (entries 4 and 5).

Attempts to use potassium bromomethyltrifluoroborate with $SiCl_4$ as the fluorophile to produce 2-bromomethyl-2,1-borazaronaphthalene (**1f**) resulted in a mixture of 2-chloromethyl-2,1-borazaronaphthalene and 2-bromomethyl-2,1-borazaronaphthalene, perhaps through displacement of bromide by chloride through an intramolecular nucleophilic substitution in the cyclization step (Scheme 1). The replacement of $SiCl_4$ with

Scheme 1. Proposed Mechanism for the Formation of 2-Chloromethyl-2,1-borazaronaphthalene (1a) from the Reaction of 2-Aminostyrene with Potassium Bromomethyltrifluoroborate

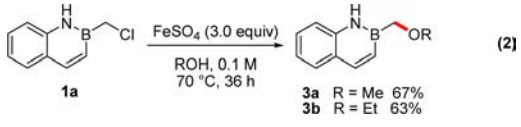


$SiBr_4$ permitted the synthesis of 2-bromomethyl-2,1-borazaronaphthalene in 65% yield (eq 1). Further studies focused on the use of 2-chloromethyl-2,1-borazaronaphthalene because the milder fluorophile was easier to handle and more tolerant of embedded functional groups.



With the pseudobenzylic chloride in hand, we investigated its use as an electrophile in substitution reactions. Nine different cyclic and acyclic amines proved to be suitable nucleophiles, affording the desired pseudobenzylic amines in yields up to 96% under mild reaction conditions (Table 2). The sterically hindered diisobutylamine provided the desired product in 69% yield (entry 2). Nonaromatic heterocyclic amines, such as piperidine, morpholine, and thiomorpholine, afforded the desired products in yields of 87%, 94%, and 96%, respectively (entries 7−9).

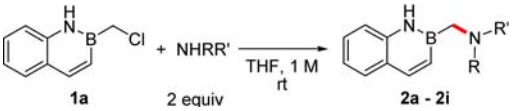
The formation of 2-alkoxymethyl-2,1-borazaronaphthalenes was next investigated. Addition of an alkoxide did not result in nucleophilic displacement of the chloride perhaps because of acid−base chemistry at the acidic N−H bond (pk ≈ 25). Consequently, an iron mediated process was employed.[6] By addition of a stoichiometric amount of $FeSO_4$, the desired ethers were synthesized in moderate to good yields. The corresponding methyl and ethyl ethers were generated in yields of 67% and 65%, respectively (eq 2).



Initial attempts to access ester-containing 2,1-borazaronaphthalenes included treating 2-chloromethyl-2,1-borazaronaphthalene with sodium carboxylates either in the presence of 18-crown-6 in toluene or without the crown ether in acetonitrile and THF at elevated temperatures, but the yield and the rate of these reactions were low. However, the reaction of 2-chloromethyl-2,1-borazaronaphthalene with an array of carboxylic acids in the presence of Cs_2CO_3 in refluxing acetonitrile afforded a variety of 2-carboxylatomethyl-2,1-borazaronaphthalenes with yields up to 92% (Table 3). Alkyl, aryl, and heteroaryl carboxylic acids all proved successful in this reaction. Interestingly, free alcohols and amides do not interfere with the esterification, as a phenol- and pyrrolidone-containing carboxylic acids were easily esterified in 68% and 79% yield, respectively (entries 3 and 6). The advantage of this method is that a variety of commercially available carboxylic acids can be employed without having to preform or purchase the corresponding carboxylate salts. Attempts to saponify the esters generated to access the corresponding hydroxymethyl borazines were unsuccessful, perhaps due to the aforementioned acid−base chemistry.

Sulfide derivatives of the 2,3-borazaronaphthalenes were also synthesized in good yields by the reaction of 2-chloromethyl-2,1-borazaronaphthalene with diorgano disulfides under mild conditions at room temperature (Table 4). These reactions were completed in the presence of Zn dust in 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIMBF_4$).[7] Four different diaryl disulfides afforded the desired products in yields up to 87%.

Table 2. Scope of the Synthesis of 2-Aminomethyl-2,1-borazaronaphthalenes



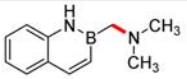
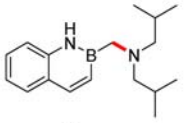
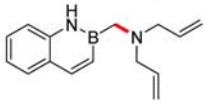
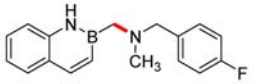
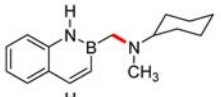
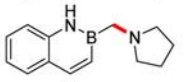
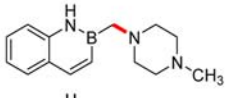
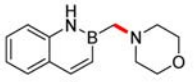
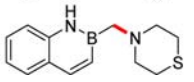
entry	product		% yield
1		**2a**	93
2		**2b**	69
3		**2c**	95
4		**2d**	89
5		**2e**	94
6		**2f**	88
7		**2g**	87
8		**2h**	94
9		**2i**	96

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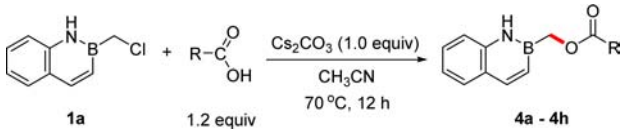
Table 3. Scope of the Synthesis of 2-Carboxylatomethyl-2,1-borazaronaphthalenes



1a 1.2 equiv 4a - 4h

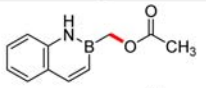
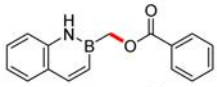
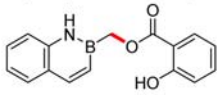
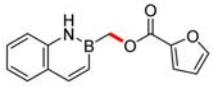
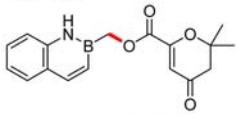
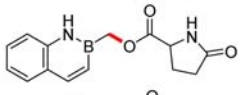
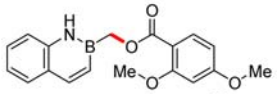
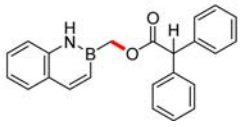
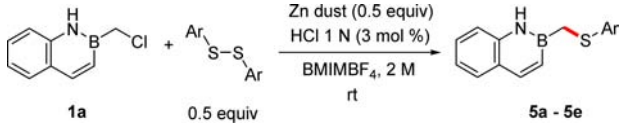
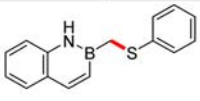
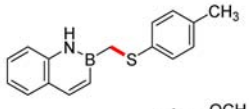
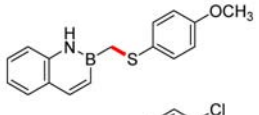
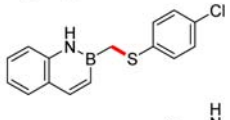
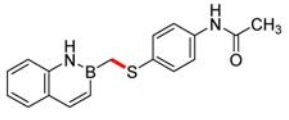
entry	product		% yield
1		4a	88
2		4b	90
3		4c	68
4		4d	90
5		4e	68
6		4f	79
7		4g	84
8		4h	92

Table 4. Scope of the Synthesis of 2-Arylsulfidomethyl-2,1-borazaronaphthalenes

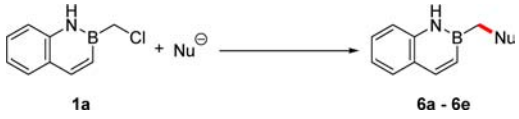


1a 0.5 equiv 5a - 5e

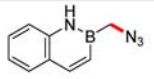
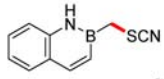
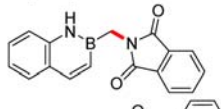
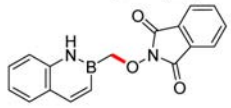
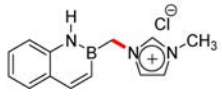
entry	product		% yield
1		5a	82
2		5b	80
3		5c	70
4		5d	87
5		5e	69

2-Chloromethyl-2,1-borazaronaphthalene can serve as the electrophile with an array of other nucleophiles, including azide, thiocyanate, phthalimide, *N*-oxyphthalimide, and 1-methylimidazole, in yields up to 90% (Table 5). For reasons that remain unknown, numerous attempts to employ cyanide as a nucleophile proved unsuccessful.

Table 5. Scope of the Nucleophilic Compatibility



1a 6a - 6e

entry	product		% yield
1		6a	85[a]
2		6b	89[b]
3		6c	82[c]
4		6d	90[d]
5		6e	68[e]

[a]1 equiv of **1a**, 1.2 equiv of NaN_3, dry CH_3CN (0.1 M), 76 °C, 2 h. [b]1 equiv of **1a**, 1.5 equiv of NaSCN, dry CH_3CN (0.1 M), 76 °C, 1 h. [c]1 equiv of **1a**, 1.2 equiv of potassium phthalimide, 10 mol % of 18-crown-6, dry toluene (0.2 M), 100 °C, 1 h. [d]1 equiv of **1a**, 1 equiv of Na_2CO_3, DMF/CH_3CN/H_2O (0.15 M), 25 °C, 12 h. [e]1 equiv of **1a**, 1.01 equiv of 1-methylimidazole, dry THF (0.2 M), 25 °C, 12 h.

Owing to the success of functionalizing 2-chloromethyl-2,1-borazaronaphthalene, we believed that 2-azidomethyl-2,1-borazaronaphthalene could serve as a triazole precursor. The click reaction[8a,b] of 2-azidomethyl-2,1-borazaronaphthalene with terminal alkynes was thus investigated as a way to build molecular complexity and install heterocyclic substituents onto an azaborine core (Table 6). The reaction proceeded under mild reaction conditions, with the corresponding triazoles being generated in high yield at room temperature. Both aryl- and alkenyl-substituted terminal alkynes provided the desired products. These cyclization reactions demonstrate the stability of 2-azidomethyl-2,1-borazaronaphthalene in metal-catalyzed reactions and aqueous reaction conditions.

Although the C−C analog of 2-chloromethyl-2,1-borazaronaphthalene, 2-chloromethylnaphthalene, is commercially available, the installation of a benzylic halide in more elaborated systems often requires free-radical halogenation of a methyl group.[9a−f] The route developed herein results in a site-selective installation of a pseudobenzylic halide, overcoming the limitations of harsh reaction conditions and regioselectivity for the addition of the halide. By not requiring prefunctionalization, a one-step synthesis of 2-chloromethyl-2,1-borazaronaphthalene affords an azaborine with a handle for further functionalization. To the best of our knowledge, this azaborine is the first azaborine synthesized with a pseudobenzylic halide, which serves as a precursor for the synthesis of a family of amines, esters, and

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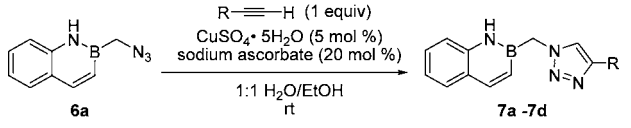
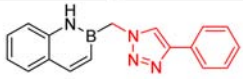
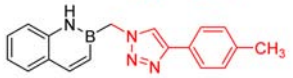
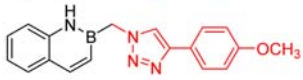
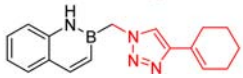
Table 6. Click Reaction of 2-Chloromethyl-2,1-borazaronaphthalene with Terminal Alkynes



entry	product		% yield
1		7a	80
2		7b	84
3		7c	79
4		7d	90

ethers from one common starting compound. 2-Chloromethyl-2,1-borazaronaphthalene has been shown to be a suitable electrophile in a variety of reactions, the products of which can be further transformed to build more elaborate azaborines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, 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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