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Toward Efficient Nucleophilic Azaborine Building Blocks for the Synthesis of B−N Naphthyl (Hetero)arylmethane Isosteres

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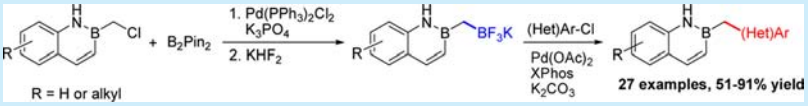
Supporting Information



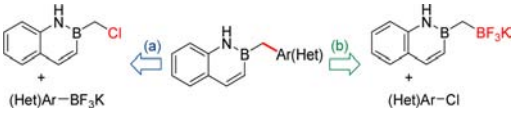
ABSTRACT: To develop a method for the synthesis of a class of azaborines, potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalenes have been synthesized to serve as nucleophilic building blocks. In palladium-catalyzed cross-coupling reactions with (hetero)aryl chlorides they serve to produce a variety of pseudobenzylic (hetero)aryl substituted azaborines. Potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalenes are crystalline solids that are more stable than 2-(chloromethyl)-2,1-borazaronaphthalenes and have a broader substrate scope in cross-coupling reactions compared to their pseudobenzylic chloride counterparts.

Isosteric replacement is a fundamental concept in synthetic chemistry and most frequently used to explore bioactive compounds in novel chemical space[1] and improve drug candidate properties. B−N/C=C isosterism has recently emerged as a practical method to increase structural diversity, as the B−N unit is both isoelectronic and isosteric with C=C bonds.[2] In particular, azaborines that are the B−N isosteres of arenes have attracted much attention in medicinal chemistry.[3] Consequently, facile methods for the synthesis of diverse arene isosteres could have an impact in the discovery of new drugs and biologically active structures. Along these lines, we have developed the synthesis of 2-(chloromethyl)-2,1-borazaronaphthalene as a versatile precursor for the synthesis of a variety of B−N isosteres of benzylic amines, ethers, thioethers, and esters.[4]

In furtherance of these efforts, attention was turned toward B−N isosteres of diarylmethanes, because it appeared likely that such systems might possess advantages over the parent diarylmethanes in terms of favorable ADME properties. Diarylmethanes are prominent structural constituents of biologically active compounds.[5] However, as a result of the propensity of diarylmethanes to undergo facile benzylic oxidation, ordinarily these structures are not ideal drug candidates. In 2013, Heider reported that the *N*- and *B*-ethyl-1,2-azaborines were strong inhibitors of ethylbenzene dehydrogenase enzyme, because in these azaborines the energies for both radical and carbocation formation at the pseudobenzylic position are substantially higher than those for ethylbenzene.[6] Extrapolating to diarylmethanes, by analogy the B−N isosteres of these substructures could also possess a higher energy of activation for oxidation at their pseudobenzylic position. Also, in the borazaronaphthalene isostere series, the positions of electrophilic substitution are complementary to those of the parent all-carbon system and highly site specific.[7] On the basis of these findings, the synthesis of B−N isosteres of diarylmethanes was anticipated to provide a pathway to the utilization of diarylmethane derivatives in pharmaceutical chemistry and agrochemistry.

Using organotrifluoroborate cross-coupling, there are two main retrosynthetic disconnection routes to synthesize 2,1-borazaronaphthyl (hetero)arylmethanes (Scheme 1). In the first route the desired 2,1-borazaronaphthyl (hetero)-arylmethane could be obtained by metal-catalyzed cross-coupling of 2-(chloromethyl)-2,1-borazaronaphthalene as an electrophile with nucleophilic potassium (hetero)-aryltrifluoroborates. In the second route, potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalene would be used instead of 2-(chloromethyl)-2,1-borazaronaphthalene as the pseudobenzylic reaction partner. In this scenario the azaborine building block acts as a nucleophile and is treated with (hetero)aryl chlorides to produce the B−N isosteres of diarylmethanes.

Scheme 1. Retrosynthetic Disconnection Routes to Synthesize 2,1-Borazaronaphthyl (Hetero)arylmethanes



We previously reported the synthesis of a variety of 2,1-borazaronaphthyl (hetero)arylmethanes as the B−N diarylmethane isosteres using 2-(chloromethyl)-2,1-borazaronaphthalene in a cross-coupling reaction.[8] Although this protocol proved highly effective, the creation of a library of 2,1-borazaronaphthyl (hetero)arylmethanes would require the

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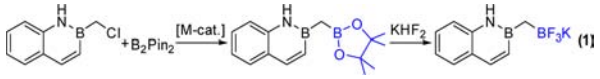
synthesis of a wide variety of aryl- and heteroaryltrifluoroborates. From a strategic viewpoint, the use of potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalene as a nucleophilic building block would have an advantage, because in such a protocol the much more widely available aryl halides could be utilized as coupling partners. Herein, the realization of this approach to the synthesis of B−N naphthyl (hetero)arylmethanes by palladium-catalyzed cross-coupling reactions is reported.

The investigation began by examining the synthesis of the potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalene derivatives. Classically, benzylboronic acid derivatives have been generated via indirect methods such as borylation of benzylmetals,[9] homologation of arylboranes,[10] and cross-couplings of arylstannanes with bromoethylboronates[11] or haloarenes with borylmethylzinc reagents.[12] More recently, significant progress has been made toward direct nucleophilic borylation of benzylic halides with the development of milder methods using transition metal-catalyzed reactions to generate benzylboronic ester derivatives.[13] For the synthesis of potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalene, the palladium-catalyzed nucleophilic borylation of 2-(chloromethyl)-2,1-borazaronaphthalene with bis(pinacolato)diboron (B_2Pin_2) was investigated. This transformation was anticipated to produce pinacol (2,1-borazaronaphthyl)methylboronate, which could be easily converted to the corresponding potassium organotrifluoroborate using saturated aqueous KHF_2 according to published methods eq 1.[14]

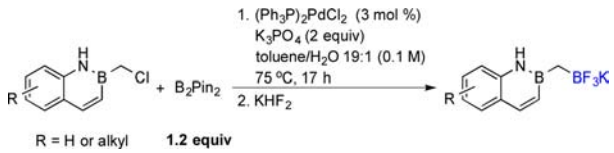


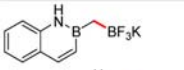
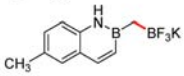
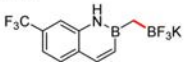
To pursue this goal using 2-(chloromethyl)-2,1-borazaronaphthalene with B_2Pin_2 as a model reaction, a wide variety of catalyst and ligand combinations, solvents, and bases were screened.[15] Investigations revealed that using 3 mol % of $(Ph_3P)_2PdCl_2$ in combination with K_3PO_4 in toluene/H_2O (19:1, 0.1 M) at 75 °C provided the best conditions. Because the tricoordinate boron species proved relatively unstable,[16] the crude reaction mixtures were treated with aqueous KHF_2 to obtain the more robust potassium trifluoroborate salt (**1a**) without purification of the pinacol (2,1-borazaronaphthyl)-methylboronate intermediate. Therefore, 2-(chloromethyl)-2,1-borazaronaphthalene was treated with B_2Pin_2 in a very straightforward procedure followed by the addition of aqueous KHF_2, which produced **1a** with 62% overall yield (Table 1, entry 1).

To demonstrate the versatility of this protocol, the reaction was extended to the borylation of substituted 2-chloromethyl-2,1-borazaronaphthalenes. Thus, the reactions of 6-methyl-2-(chloromethyl)-2,1-borazaronaphthalene and 7-trifluoromethyl-2-(chloromethyl)-2,1-borazaronaphthalene were carried out with B_2Pin_2, demonstrating that substitution on the ring does not affect the borylation. The corresponding products were isolated in 54% and 60% overall yields, respectively (entries 2 and 3).

The borazaronaphthalene derivatives prepared in this manner proved more stable and robust than their 2-(chloromethyl)-2,1-borazaronaphthalene analogues. Additionally, they are free-flowing, colorless, crystalline solids, further facilitating their handling and storage (Figure 1).

Table 1. Scope of the Synthesis of Potassium 2-(Trifluoroboratomethyl)-2,1-borazaronaphthalenes[a]



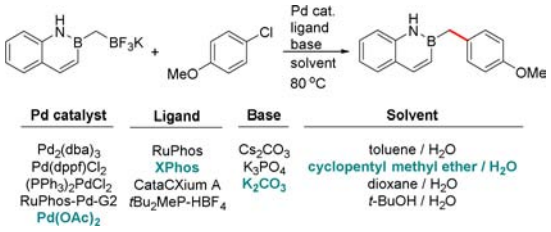
entry	product		% yield[b]
1		**1a**	62
2		**1b**	54
3		**1c**	60

[a]Reactions completed on a 2 mmol scale. [b]The overall yield after two steps.

Figure 1. (a) 2-(Chloromethyl)-2,1-borazaronaphthalene; (b) **1a**.

Upon synthesizing the pseudobenzylic trifluoroborates, we investigated their reactivity as nucleophiles in Suzuki−Miyaura cross-coupling reactions with aryl- and heteroaryl chlorides. Substrates **1a** and 4-chloroanisole were chosen as coupling partners to uncover suitable reaction conditions. Using microscale high-throughput experimentation (HTE),[17] the cross-coupling reaction was screened extensively with different palladium catalysts, ligands, bases, solvents, and concentrations (Scheme 2).[15] This study revealed that the combination of 2

Scheme 2. Microscale HTE Screening for Optimal Reaction Conditions of 1a with 4-Chloroanisole



mol % of $Pd(OAc)_2$, 4 mol % XPhos as a ligand and 2 equiv of K_2CO_3 in cyclopentyl methyl ether (CPME)/H_2O solvent mixture (19:1) at 80 °C provided an excellent outcome, giving the highest yield of 2-(4-methoxybenzyl)-2,1-borazaronaphthalene analysis by HPLC. Further investigations showed that increasing the concentration of the reaction from 0.1 to 0.2 M led to a further increase in the yield of the reaction.

Using these conditions, **1a** cross-coupled with 4-chloroanisole in 80% isolated yield (Table 2, entry 1). Subsequently, to investigate the substrate scope of these optimized conditions we applied the conditions to the cross coupling reaction of **1a** as the nucleophilic partner with various substituted aryl chlorides (Table 2). All of the aryl chlorides utilized were successfully cross-coupled to give the corresponding products in yields of 54−91%. In general, electron-neutral aryl chlorides

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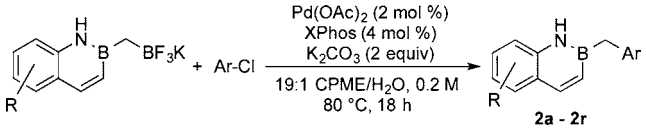
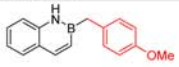
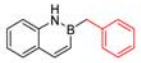
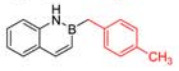
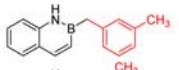
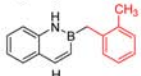
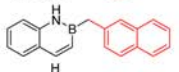
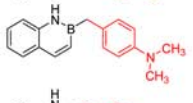
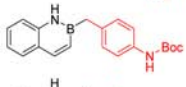
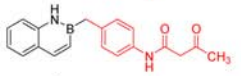
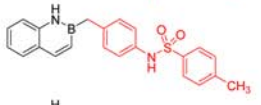
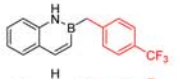
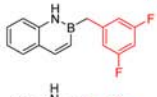
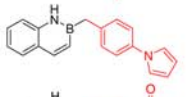
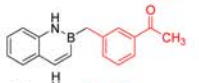
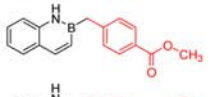
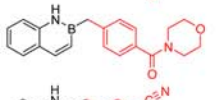
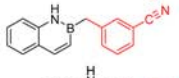
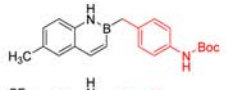
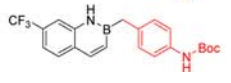
Table 2. Scope of the Cross-Coupling with Aryl Chlorides



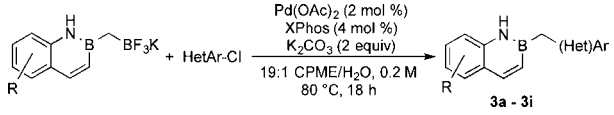
entry	product		% yield
1		2a	80 (72)[a]
2		2b	90
3		2c	91
4		2d	84
5		2e	78
6		2f	91
7		2g	89
8		2h	89
9		2i	63
10		2j	54
11		2k	61
12		2l	75
13		2m	85
14		2n	82
15		2o	73
16		2p	61
17		2q	82
18		2r	81
19		2s	79

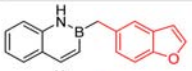
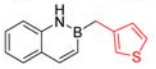
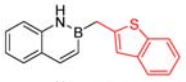
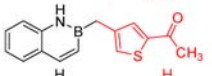
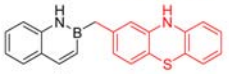
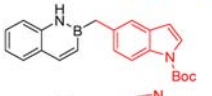
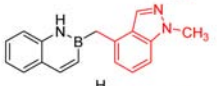
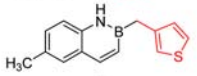
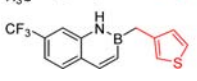
[a]Reaction completed on 4.5 mmol scale with 1.5 mol % $Pd(OAc)_2$.

(entries 2–6) and aryl chlorides containing electron-donating groups (entries 1 and 7–8) were slightly better substrates than those possessing electron-withdrawing groups (entries 11–16). Aryl chlorides containing a methyl group in the para (entry 3), meta (entry 4), and ortho (entry 5) positions afforded the desired cross-coupled products in good yields. Interestingly, several functional groups such as amines, ketones, sulfonamides, β-dicarbonyls, esters, amides, and nitriles were compatible with the reaction conditions and provided the desired products in good yields (entries 10, 15–17). To explore the scope of the method further and to show the versatility of this method toward substituted potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalenes, the cross coupling reactions of potassium 6-methyl-2-(trifluoroboratomethyl)-2,1-borazaronaphthalene (**1b**) and potassium 7-trifluoromethyl-2-(trifluoroboratomethyl)-2,1-borazaronaphthalene (**1c**) as the nucleophilic partners with 4-chloro-(*N*-boc)aniline were carried out. The corresponding products were isolated in yields of 81% and 79%, respectively (Table 2, entries 18 and 19). To demonstrate the scalable nature of the cross-coupling, a reaction on the 4.5 mmol scale with 1.5 mol % $Pd(OAc)_2$ was performed, which provided the desired product in 72% yield (entry 1).

The scope of the electrophiles was then expanded to a variety of heteroaryl chlorides (Table 3). Oxygen-, sulfur-, and

Table 3. Scope of the Cross-Coupling with Heteroaryl Chlorides



entry	product		% yield
1		3a	75
2		3b	79
3		3c	60
4		3d	76
5		3e	51
6		3f	91
7		3g	57
8		3h	57
9		3i	49

nitrogen-containing heteroaryl chlorides were found to be good coupling partners, and **1a** was efficiently coupled with them with good yields. In the case of indoles and indazoles, *N*-protected or *N*-alkyl substituted derivatives were required (entries 6 and 7). The desired products were not formed unless the nitrogen of the electrophilic heteroaryl halide was protected. Finally, substituted borazaronaphthalenes (**1b** and **1c**) were successful nucleophiles for the coupling with heteroaryl chlorides (Table 3, entries 8 and 9).

In conclusion, a class of borazaronaphthalene derivatives, potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalenes, has been synthesized, and the utility of these borazaronaphthalene derivatives as nucleophiles in palladium-catalyzed cross-

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coupling reactions with (hetero)aryl chlorides has been described. This cross-coupling reaction has a broad substrate scope with good to excellent yields. In fact, this nucleophilic azaborine derivative is a versatile precursor for the synthesis of a variety of borazaronaphthyl arylmethanes. Because of the scope of this cross-coupling reaction and also the stability of this class of compounds, they can be considered as efficient precursors for the facile synthesis of the azaborine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, HTE data, compound characterization data, and NMR spectra for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01750.

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Notes

The authors declare no competing financial interest.

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