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Expanding the functional group tolerance of cross-coupling in 1,2-dihydro-1,2-azaborines: installation of alkyl, alkenyl, aryl, and heteroaryl substituents while maintaining a B–H bond.

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Abstract

Palladium-catalyzed Negishi cross-coupling of 3-bromo-1-(tert-butyldimethylsilyl)-1,2-dihydro-1,2-azaborine while maintaining the B–H functionality has been demonstrated. 17 examples, including dialkylzinc, alkyl-, alkenyl-, aryl-, as well as nitrogen-, sulfur-, and oxygen-containing heteroaryl-zinc halide reagents have been coupled to generate new C(3) substituted 1,2-azaborines in moderate to excellent yields.

Graphical Abstract

1,2-Dihydro-1,2-azaborines are BN/C=C isosteres of the ubiquitous benzene motif [1]. Dewar and White sparked interest in these heterocycles in the fields of materials and biomedical science through their pioneering work with BN-arenes in the early 1960's [2]. At the turn of the century, Ashe revitalized the field through the use of modern synthetic methods [3], and later demonstrated the regioselective electrophilic aromatic substitution of 1,2-azaborines [4]. Our fundamental contributions to 1,2-azaborine chemistry include the synthesis of the long-sought parental 1,2-dihydro-1,2-azaborine [5], the investigation of the aromatic character of this heterocycle [6], and the development of the 1,2-azaborine heterocycle as a new pharmacophore in drug discovery research [7]. The enabling linchpin precursor for our work is the now commercially available *N*-TBS,*B*-Cl-1,2-azaborine synthon **1** [8], which can be readily substituted at boron position [9].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tet.xxxx>.

We aim to expand the utility of 1,2-azaborine motif by developing late-stage functionalization strategies that will enable the rational synthesis of new BN-containing compounds. Metal-catalyzed cross-coupling is a powerful strategy for versatile and mild carbon-carbon bond forming reactions and has revolutionized modern synthesis [10]. Molander [11] and Fang [12] have established the use of cross-coupling strategies for late-stage functionalization of halogenated ring-fused boron-substituted 2,1-borazaronaphthalenes and 9,10-borazaronaphthalenes respectively (Scheme 1). Our group has begun to explore cross-coupling strategies for monocyclic 1,2-azaborines. To this end, we have demonstrated Suzuki cross-coupling of 6-Bpin-1,2-dihydro-1,2-azaborine at the C(6) position with aryl bromides [13]. The scope of this cross-coupling, however, is limited and has not been established for alkyl bromides, for example. We have also shown that the B-Cl bond in the triply-orthogonal 1,2-azaborine **2** is compatible to Negishi cross-coupling conditions of alkyl-, alkenyl-, and electron deficient aryl-zinc halides (Scheme 1) [14].

We were interested in expanding the scope of cross-coupling partners beyond the limited examples demonstrated with compound **2**, as well as exploring the effect, if any, that the B-H substituent would have on the Negishi cross-coupling at the C(3) position. Compound **3** was stable to treatment with excess diethylzinc for 24 hours at room temperature and for over 1 hour at 100 °C, which is similar to the observed stability of compound **2**. We selected propylzinc bromide as a model nucleophile due to the lower reactivity and higher availability of alkylzinc halide reagents compared to dialkylzinc reagents. In order to develop this reaction we screened a variety of electron rich and sterically hindered phosphines (Table 1) for their activity in our model system. We hoped to determine alternatives to the relatively expensive $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ catalyst which was the most effective catalyst for cross coupling of **2**. Mixed alkyl/aryl phosphines (Table 1, entries 1–4) showed similar activity to the electron-rich $\text{P}(\text{cy})_3$ and the sterically hindered $\text{P}(\text{tol})_3$ (Table 1, entries 5 and 7, respectively). Of the phosphines screened, $\text{P}(\text{furyl})_3$ showed the lowest yield of expected product (Table 1, entry 6). Trialkylphosphonium phosphine precursors [15] were also active in this transformation (Table 1, entries 8 and 9) while $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ showed a relatively low yield for the model reaction (Table 1, entry 10). None of the catalysts screened showed a large increase in yield for this cross-coupling, so we optimized this reaction with $\text{PdCl}_2(\text{P}^t\text{ol}_3)_2$ for operational and economic simplicity, generating a 75% GC yield of **4a** in 1 hour at 50 °C (table 1, entry 11) [16].

With optimized conditions in hand for the synthesis of **4a** we applied these conditions to other alkylzinc halide and dialkylzinc reagents as shown in Scheme 2 in order to generate C(3) substituted azaborines **4a-e**. In order to ensure completion, we held each reaction at 50 °C for 1.5 hours as opposed to 1 hour. Gratifyingly, the reaction with propylzinc bromide gave a higher isolated yield upon scale up than that observed during optimization (**4a**, 85%). Dimethyl zinc (**4b**, 81%) and diethyl zinc (**4c**, 81%) coupled in good yield without evidence of alkylation at boron, while alkylzinc bromides with either alkyl chloride (**4d**, 64%) or acetal (**4e**, 64%) functionalities proceeded in moderate yield [17].

Unfortunately, under identical conditions our preliminary attempts to cross-couple arylzinc halides were not clean or high-yielding. Organ has extensively studied the mechanism and reactivity of alkyl- and aryl-zinc halides and has shown that maximizing reactivity can

require separate conditions for alkyl- and aryl-zinc reagents [18]. In our system, a return to the $\text{Pd}(\text{P}^t\text{Bu}_3)_2$ catalyst system was sufficient to facilitate the cross-coupling reactions of alkenyl, aryl, and heteroaryl zinc compounds generating C(3) substituted azaborines **4f-4q** in moderate to excellent yields as shown in Scheme 3.

Phenylzinc bromide couples in good yield (**4f**, 73%), while electron rich 4-methoxy phenylzinc bromide (**4g**, 75%) and electron deficient 4-fluorophenylzinc bromide (**4h**, 56%) are also viable coupling partners. Sterically hindered 2,4,6-trimethylphenylzinc iodide coupled sluggishly in good yield (**4i**, 74%). Aryl-halide containing 4-chlorophenylzinc bromide (**4j**, 89%) and 4-bromophenylzinc iodide (**4k**, 57%) were also amenable to these conditions, and could be substrates for further cross-coupling [19]. 2,3-Methylenedioxyphenylzinc iodide (**4l**, 96%), 4-cyanophenylzinc bromide (**4m**, 91%) and alkenyl (1-phenylvinyl)zinc bromide (**4n**, 94%) coupled in excellent yield. Cross-coupling with 4-coumarinylzinc bromide generates the neoflavone [20] structure in good yield (**4o**, 75%) providing an example of an oxygen-containing heterocycle. We were successful in coupling both isoquinoline- (**4p**, 88%) and thiophene- (**4q**, 85%) containing zinc reagents in good yield as examples of nitrogen and sulfur containing heterocycles. We were unable to cross-couple electron rich arenes in the presence of a B–Cl bond in our previous study of cross-coupling with compound **3** as they generated a mixture of B–O species.[14] The increased stability of the B–H bond to nucleophiles allows for a wider range of coupling partners; however the attempted cross-coupling of allylzinc bromide gave a mixture of B-alkylated products showing a dependence on the nature of the zinc nucleophile for successful cross-coupling in these systems.

We were able to grow crystals suitable for single crystal x-ray diffraction of **4l** as shown in Figure 2. The bond lengths in the azaborine ring are in agreement with those in B,-N-disubstituted 1,2-azaborines.[9b] The C(4)-C(5) bond length of 1.485 is similar to that in biphenyl [21]. The dihedral angle is 37.5° which is consistent with expected angles for typical biaryl compounds.

In summary, we have demonstrated a versatile functionalization strategy through the use of Negishi coupling for the installation of alkyl, aryl, alkenyl, and heteroaryl substituents while maintaining a B–H bond of brominated 1,2-azaborine **3**. This cross-coupling tolerates aryl and alkyl chlorides; acetals; as well as sulfur, nitrogen, and oxygen containing heterocycles. We are continuing to explore this methodology in order to expand the accessible 1,2-azaborine structures to enable their use in ligand design, materials science, and biomedical research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Figure 1:
N-TBS, *B*-Cl-1,2-Azaborine **1**

Figure 2. ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level of **4i**; all hydrogen atoms (except of the B-H) have been omitted for clarity.

Scheme 2: Negishi cross-coupling of 3 with alkyl- and dialkyl- zinc reagents.

Percent yields are isolated and the average of two runs. ^a Dialkylzinc (1.5 equiv) used

^b Alkylzinc bromide (1.5 equiv) used.

Scheme 3: Negishi cross-coupling of 3 with aryl-, alkenyl-, and heteroaryl-, zinc halide reagents. Percent yields are isolated and the average of two runs. ^a conditions: 3 equiv 2,4,6-trimethylphenylzinc iodide, 0.05 equiv $Pd(P^tBu_3)_2$, THF, rt, 48 h. ^b 4-bromophenylzinc iodide was used. ^c 2,3-Methylenedioxyphenylzinc iodide was used.

Table 1:

Optimization of B–H tolerant Negishi cross-coupling.

Entry	Pd Source	Ligand	% yield ^a
1	$\text{PdCl}_2(\text{PhCN})_2$	P^tBuPh_2	75
2	$\text{PdCl}_2(\text{PhCN})_2$	$\text{P}(\text{cy})_2\text{mes}$	70
3	$\text{PdCl}_2(\text{PhCN})_2$	$\text{P}(\text{cy})_2\text{Ph}$	75
4	$\text{PdCl}_2(\text{PhCN})_2$	orthobiphenyl P^tBu_2	73
5	$\text{PdCl}_2(\text{PhCN})_2$	$\text{P}(\text{cy})_3$	76
6	$\text{PdCl}_2(\text{PhCN})_2$	$\text{P}(2\text{-furyl})_3$	53
7	$\text{PdCl}_2(\text{PhCN})_2$	$\text{P}(\text{}^o\text{tol})_3$	72
8	$\text{PdCl}_2(\text{PhCN})_2$	$\text{HP}^t\text{Bu}_3^+ \text{BF}_4^-$	68
9	$\text{PdCl}_2(\text{PhCN})_2$	$\text{HP}^t\text{Bu}_2\text{Me}^+ \text{BF}_4^-$	77
10	$\text{Pd}(\text{P}^t\text{Bu}_3)_2$	-	67
11	$\text{PdCl}_2(\text{P}^o\text{tol}_3)_2$	-	75 ^b

^aPercent yield determined by GC-FID with undecane as calibrated internal standard.^bConditions: THF, 5 mol% $\text{PdCl}_2(\text{P}^o\text{tol}_3)_2$, 50 °C, 1h. Abbreviations: cy: cyclohexyl, mes: mesityl. In the absence of a Pd complex no reaction was observed at room temperature after 24h or at 50 °C after 1h.