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A Boron Protecting Group Strategy for 1,2-Azaborines

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ABSTRACT: Upon reaction with either molecular oxygen or di-*tert*-butylperoxide in the presence of a simple copper (I) salt and an alcohol, a range of 1,2-azaborines readily exchange *B*-alkyl or *B*-aryl moieties for *B*-alkoxide fragments. This transformation allows alkyl and aryl groups to serve for the first time as removable protecting groups for the boron position of 1,2-azaborines during reactions that are not compatible with the easily modifiable *B*-alkoxide moiety. This reaction can be applied to synthesize a previously inaccessible BN isostere of ethylbenzene, a compound of interest in biomedical research. A sequence of epoxide ring opening using *N*-deprotonated 1,2-azaborines followed by an intramolecular version of the boron deprotection reaction can be applied to access the first examples of BN isosteres of dihydrobenzofurans and benzofurans, classes of compounds that are important to medicinal chemistry and natural product synthesis.

1. INTRODUCTION

BN/CC isosterism of classic organic arenes[1] has emerged as a viable strategy to expand structural diversity of arenes and produce molecules with applications in biomedical research[2] and materials science.[1c,1d,3] In order to access a broad range of monocyclic 1,2-dihydro-1,2-azaborine substrates (abbreviated 1,2-azaborines), our group primarily utilizes late-stage functionalization strategies to diversify an assembled 1,2-azaborine core that is generated from a modified ring-closing metathesis route[4] pioneered by Ashe.[5] Despite recent advances including late-stage functionalization of 1,2-azaborines at the C3 position via an EAS (electrophilic aromatic substitution)/Negishi coupling sequence[6] and at the C6 position via a C-H borylation/Suzuki coupling sequence (Figure 1),[7] the development of applications of these heterocycles is still hampered by the lack of further viable functionalization strategies.

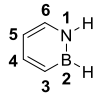
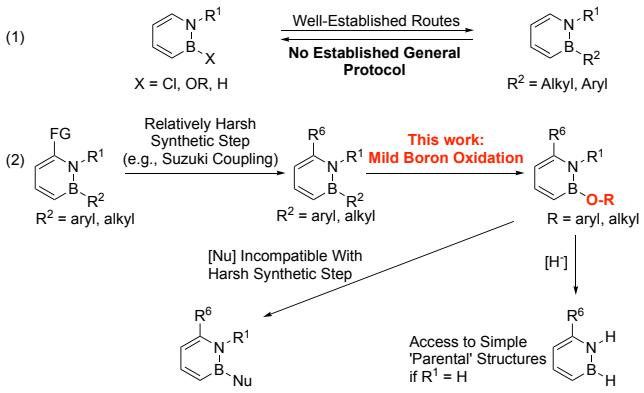


Figure 1. Ring position labeling of 1,2-azaborines.

Manipulation of the boron position of azaborines forms the core of our synthetic efforts as the nature of the boron substituent greatly influences properties of azaborines such as solubility, volatility, stability towards air and moisture,[8] reactivity towards nucleophiles, and stability during the course of relatively harsh transformations such as Suzuki coupling. For example, *C6*-B(pin) azaborines bearing alkyl or aryl groups at the ring boron position react exclusively at the B(pin) moiety during Suzuki couplings with a diverse range of aryl bromide coupling partners, but *C6*-B(pin) azaborines bearing alkoxy groups or hydrogen at the ring boron position only tolerate a greatly restricted set of cross coupling conditions and coupling partners.[7] Conversely, azaborines bearing alkoxy groups, chloride, or hydrogen at boron readily react at boron via nucleophilic addition/elimination,[4,9,10] rhodium catalyzed arylation,[11] or rhodium catalyzed dehydrogenative borylation,[12] whereas azaborines bearing alkyl or aryl groups at boron do not undergo these reactions.

Scheme 1. Removal of B-alkyl or B-aryl groups from azaborines

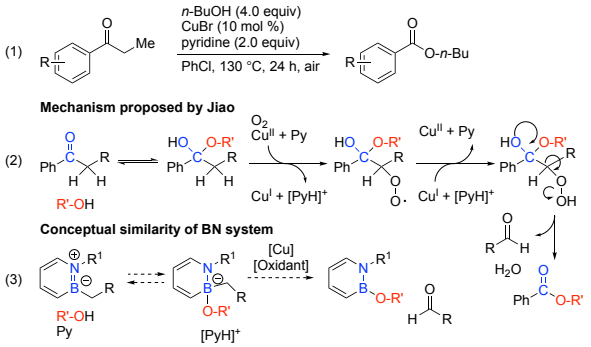


In contrast to the abundance of available transformations of *B*-alkoxy, *B*-Cl, or *B*-H azaborines into *B*-alkyl or *B*-aryl azaborines, previous examples[13] of the reverse transformation are restricted to polycyclic azaborines and are narrow in scope (Scheme 1, eq. 1). The development of a more general transformation for monocyclic azaborines—and perhaps for boron-containing heteroarenes of any type—is highly desirable because it would enable alkyl or aryl groups to serve as removable boron protecting groups during reaction sequences requiring synthetic steps incompatible with azaborines bearing labile substituents at boron (Scheme 1, eq. 2). We envisioned that a reasonable strategy to carry out this transformation would involve oxidative conversion of a *B*-alkyl or *B*-aryl azaborine to a versatile *B*-alkoxy azaborine.[14] Conversion of alkyl boranes to alkyl boronates through the use of hydrogen peroxide reagents[15] is a cornerstone transformation in the synthesis of alcohols from alkenes,[16] but application of similar conditions to azaborine substrates results in decomposition of the aromatic heterocycles.

A report from Jiao and coworkers describing the relatively mild copper catalyzed oxidation of aryl ketones to aryl esters using molecular oxygen as the sole oxidant caught our attention as providing a potentially viable alternative (Scheme 2, eq. 1).[17] We postulated that perceived similarities between the reactivity of the electrophilic

carbonyl carbon involved in this transformation (Scheme 2, eq. 2) and the known reactivity of the electrophilic boron atom of azaborines (Scheme 2, eq. 3) may allow an analogous transformation to occur for azaborine substrates under similar conditions using a copper (I) source and either molecular oxygen or a dialkylperoxide[18] as the stoichiometric oxidant. Herein we describe the successful application of a copper catalyzed protocol to carry out the azaborine *B*-R to *B*-alkoxy transformation while leaving the azaborine ring intact. We describe our initial investigations of the mechanistic features of this transformation, how our experiments reveal a mechanistic picture considerably different from what we expected based on the work of Jiao, and the applications of this method to access azaborines that require removal of a *B*-alkyl group as a key synthetic step.

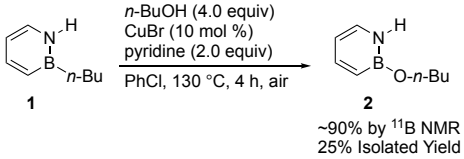
Scheme 2. Mechanistic inspiration



2. RESULTS AND DISCUSSION

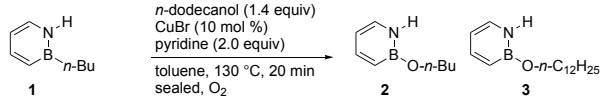
At the outset of this project, we tested the activity of the readily available *N*-H, *B*-*n*-Bu azaborine **1**[14] under conditions[17] adapted from Jiao and coworkers (Scheme 3). We were delighted to find that a ^{11}B NMR spectrum of the reaction revealed the complete consumption of *B*-butyl azaborine **1** (^{11}B shift ~ 35 ppm) and appearance of a peak corresponding with the desired *B*-butoxy material **2**[14] (^{11}B shift ~ 30 ppm) and a minor peak assigned to one or more $B(OR)_3$ species produced as undesired side products (^{11}B shift ~ 20 ppm).

Scheme 3. Initial *B*-alkyl to *B*-alkoxy transformation



Encouraged by this promising result, we explored the consequences of modifying various reaction parameters. We replaced n-butanol with n-dodecanol in the reaction for two reasons: the longer alkyl chain grants increased stability towards silica gel chromatography to the *B*-alkoxide product **3**, and we were able to distinguish products arising from incorporation of the alcohol versus those arising from potential net oxygen insertion. After brief preliminary reaction optimizations including a wide survey of alternate metal salts in place of copper (I) bromide (Tables S1 and S2) resulting in the standard conditions shown in Entry 1 of Table 1, we confirmed that a supply of oxygen was necessary for reactivity (entries 1-2) and that a sealed system with pure oxygen led to a cleaner reaction than those run sealed with air or performed open to air at reflux (entries 3-4). Removing the *n*-dodecanol additive from the system led to an inefficient production of **2**, indicating that a net oxygen insertion is operative to some extent in production of this species (entry 5). Adding *n*-butanol to the reaction granted **2** in a yield comparable to the total yield of *B*-OR material obtained from the standard reaction conditions, demonstrating that an alcohol additive is essential to achieve a relatively clean reaction (entry 6). Removing the copper (entry 7) or everything besides **1**, the solvent, and oxygen (entry 8) resulted in high conversion of **1** but poor yield of *B*-OR compounds **2** or **3**, showing a largely unfavorable direct reaction between molecular oxygen and the azaborine[19] that was either suppressed or outpaced in the presence of the copper and alcohol additives. The *B*-OR products demonstrated a high degree of oxygen stability compared to that of *B*-alkyl **1**, since the yield of **2** and **3** remained high after extended reaction time (entry 9). Finally, adding BHT (butylated hydroxytoluene) to the reaction strongly suppressed the conversion of **1** to any product or byproduct, suggesting that radical pathways are essential to the conversion of **1** in the presence of molecular oxygen (entry 10).

Table 1. Reaction using molecular oxygen as oxidant



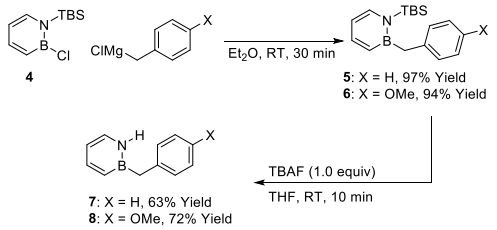
Entry	Change from Standard Conditions	Conversion of **1** (%)[a]	Yield of **2** (%)[a]	Yield of **3** (%)[a]
1	none	94	15	64
2	nitrogen atmosphere	2	0	0
3	air	44	4	32
4	air, reflux	53	5	42
5	*n*-dodecanol removed	77	25	0
6	*n*-butanol instead of *n*-dodecanol	89	73	0
7	CuBr removed	79	5	39
8	CuBr, alcohol, and pyridine removed	74	14	0
9	reaction run for two hours	100	14	64
10	BHT (2.0 equiv) added	5	0	4

[a] Conversion and yield obtained by GC using dodecane as a calibrated internal standard

Although we demonstrated that the desired *B*-R to *B*-OR transformation was possible under the aerobic conditions inspired by Jiao and coworkers, the best yields were only modest due to competitive decomposition of the azaborine material to $B(OR)_3$ species during the course of the reaction. Furthermore, we failed to detect any aldehyde byproducts that would be expected if the mechanism proposed by Jiao was operative in our case, and suspected the carbon leaving group on the azaborine may instead be expelled as a radical during the progress of the reaction. The lessons we learned from these aerobic reactions guided us to explore an alternate system. First, we used di-*tert*-butylperoxide (DTBP)[20] under a nitrogen atmosphere as the oxidant to potentially reduce the prevalence of unwanted side reactions between the azaborine substrate and molecular oxygen. Second, we examined the benzyl group as the boron leaving group, since it should impart the same stability towards cross coupling or other nucleophilic reaction conditions that *n*-butyl would, and it would become a relatively stable radical species in case this expulsion contributed to limiting the rate of the overall reaction.

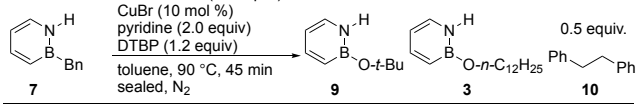
Our synthesis of *B*-benzyl azaborines followed straightforward protocols involving addition of a benzyl Grignard reagent to *N*-TBS, *B*-Cl azaborine **4**[4] to generate the *N*-TBS, *B*-benzyl azaborines **5** and **6** on gram scale in excellent yield. Both could undergo silyl deprotection with TBAF in good yield on gram scale to yield *N*-H, *B*-benzyl azaborines **7** and **8** (Scheme 4).

Scheme 4. Generation of *B*-benzyl azaborines



With *N*-H, *B*-benzyl substrate **7** in hand, we investigated the new set of conditions as illustrated in Table 2. Switching oxidants and substrates resulted in a cleaner transformation to the desired product **3** with only a small amount of the *B*-O-*t*-Bu product **9** observed and a nearly stoichiometric amount of bibenzyl **10** formed as a byproduct (entry 1). In contrast to the reaction using molecular oxygen, removal of the copper nearly completely suppressed the conversion of **7** (entry 2) and some conversion was only seen when heating the system to 130 °C (entry 3). The generation of bibenzyl was also suppressed upon removal of CuBr. Removal of pyridine or the substitution of pyridine with triethylamine or bipyridine resulted in similarly low conversions and yields for the reaction (entries 4-6). In the absence of *n*-dodecanol the *B*-O-*tert*-butyl product **9** was formed via incorporation of one half of DTBP into the azaborine (entry 7). Without the oxidant present, the desired reaction did not occur and only minimal conversion took place (entry 8). The reaction required elevated temperatures to occur (entry 9), but could be run 40 °C lower than the reactions described in Table 1. When we replaced DTBP with *tert*-butyl hydrogen peroxide (TBHP) we observed a less efficient reaction with a worse gap between conversion and yield of **3** (entry 10). We ran a small number of experiments on *B*-benzyl substrate **7** with other copper sources and with molecular O_2 as oxidant, but observed less efficient reactions in all cases (Table S3).

Table 2. CuBr/DTBP-catalyzed boron deprotection of **7**.



7 9 3 10

Entry	Change from Standard Conditions	Conversion of **7** (%)[a]	Yield of **9** (%)[a]	Yield of **3** (%)[a]	Yield of **10** (%)[a]
1	none	100	1	75	81
2	CuBr removed	1	0	0	1
3	CuBr removed, run at 130 °C	14	0	5	7
4	pyridine removed	24	0	15	23
5	NEt_3 instead of pyridine	16	0	9	16
6	bipy (1.0 equiv), no pyridine	72	1	48	60
7	*n*-dodecanol removed	81	59	0	59
8	DTBP removed	2	0	0	2
9	reaction run for 2 hours at RT	0	0	0	0
10	TBHP instead of DTBP	76	0	42	37

[a] Conversion and yield obtained by GC using dodecane as a calibrated internal standard

The experiments in Table 2 and Table S3 and the detailed mechanistic studies performed by others[18,20] prompt us to propose a tentative mechanism for the *B*-R to *B*-OR transformation using the system based on copper and DTBP (Figure 2). We propose an initial generation of a Cu(II) alkoxide species from the reaction of a Cu(I) species with the DTBP oxidant with concomitant formation of a tert-butoxide radical.[21] Next, the alkoxide radical attacks the azaborine boron atom via a one-electron pathway to generate azaborine radical **11**. We believe that the Cu metal may serve as a reservoir for the tert-butoxide radical. A Cu(I) species may then mediate the removal of the boron benzyl group to generate the azaborine product **9**, which exchanges alkoxide groups with the *n*-dodecanol in solution to generate the ultimate azaborine product **3**. The copper (II) benzyl species could finally mediate removal of a second benzyl group to generate another equivalent of **9** and a Cu(III) bisalkyl species[22] that could produce bibenzyl by reductive elimination and regeneration of a Cu(I) species.

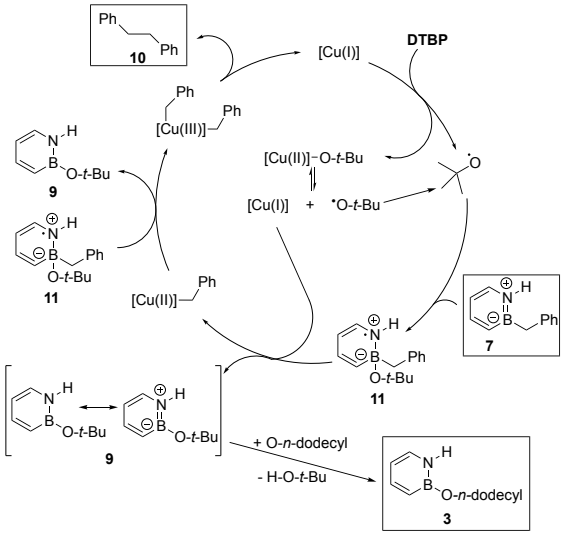
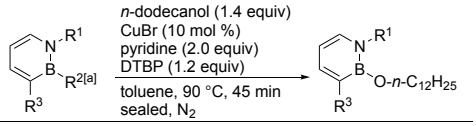
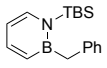
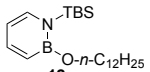
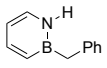
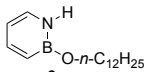
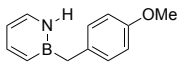
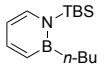
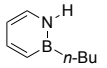
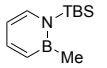
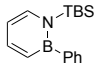
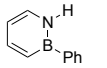
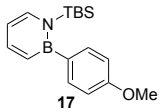
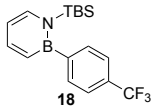
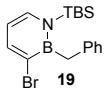
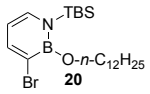
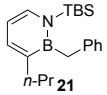
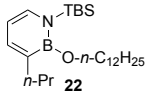


Figure 2. Plausible mechanism for the *B*-R to *B*-OR transformation

With a set of optimized reaction conditions in hand we explored the substrate scope with respect to the azaborine reagent in this transformation (Table 3). Substrates with *N*-TBS groups gave good isolated yields in comparison to those with *N*-H groups (entries 1 vs 2) likely due to the greater tendency of *N*-H, *B*-OR azaborines to bind to silica gel compared to the low silica gel affinity of the silylated substrates. The only bibenzyl species observed following the deprotection of **8** was the symmetrical product bearing two OMe groups, demonstrating that there is no crossover between the benzyl leaving group and the toluene solvent during the course of this reaction (entry 3). Azaborines bearing alkyl and aryl leaving groups also underwent the deprotection, albeit with reduced yields compared to substrates bearing benzyl groups (entries 4-10). The ability of the leaving group to stabilize a radical seems to correlate with the degree of success of the reaction. Azaborines bearing either a bromine or an *n*-propyl group at the C3-position and a benzyl leaving group underwent the reaction in modest yield (entries 11-12). Finally, an azaborine bearing a mesityl group at boron failed to undergo the reaction, likely due to the steric bulk of the mesityl group preventing nucleophilic attack at boron.

Table 3: Scope of deprotection method



Entry	Starting Material	Product	% Yield Isolated[b] (NMR)[c]
1	 **5**	 **12**	**90** (99)
2	 **7**	 **3**	**66** (97)
3	 **8**	**3**	**61** (94)
4	 **13**	**12**	**69** (70)
5	 **1**	**3**	**59** (78)
6	 **14**	**12**	**54** (66)
7	 **15**	**12**	**49** (57)
8	 **16**	**3**	**35** (57)
9	 **17**	**12**	**37** (53)
10	 **18**	**12**	**54** (59)
11	 **19**	 **20**	**40** (57)
12	 **21**	 **22**	**53** (65)

[a] Azaborines with R^2=mesityl failed to undergo the reaction [b] Isolated yields are an average of two runs. [c] NMR yields obtained using 1,5-cyclooctadiene (cod) as a calibrated internal standard. All NMR yields are an average of two runs.

With our new protocol in place for the boron deprotection of *B*-benzyl azaborines, we used this strategy as a key step in the synthesis of *C6*-ethyl BN-ethylbenzene **25** (Figure 3, eq. 1). Our group has investigated the activity of BN-ethylbenzenes **23** and **24** towards ethylbenzene dehydrogenase[2b] as well as ligands for engineered T4 lysozymes,[2a,2e] and we desire access to more regioisomers of BN-ethylbenzene to develop a systematic structure-activity relationship analysis of the effects of BN/CC isosterism in biological settings. A straightforward strategy[7] involving the cross coupling between vinyl bromide and *C6*-borylated azaborines with labile groups already installed at the boron atom failed due to the sensitivity of these azaborines towards the reaction conditions (Figure 3, eq. 2).

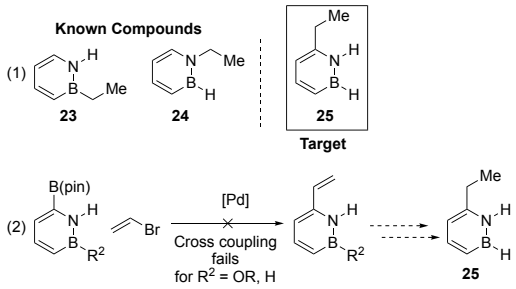
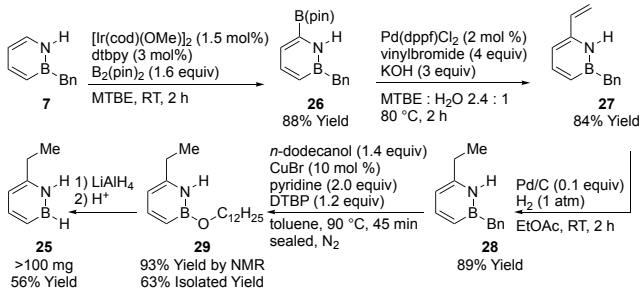


Figure 3. BN-Ethylbenzene analogs.

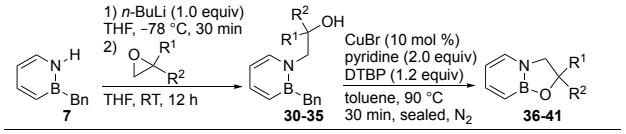
Initial borylation of *N*-H, *B*-benzyl **7** under standard iridium catalyzed borylation conditions[23] granted *C6*-B(pin) azaborine **26** in excellent yield, and this substrate underwent cross coupling without difficulty to generate *C6*-vinyl azaborine **27** (Scheme 5). Compound **27** was hydrogenated under mild conditions to produce *C6*-ethyl azaborine **28**, which cleanly underwent the boron deprotection protocol to grant access to *B*-OR azaborine **29**. As the final step in the synthesis, we reduced **29** to the target compound **25** using $LiAlH_4$ followed by a mild acid, and isolated over 100 mg of the volatile *C6*-ethyl, *N*-H, *B*-H azaborine.

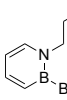
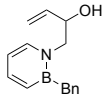
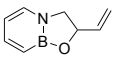
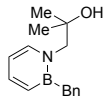
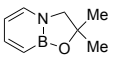
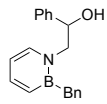
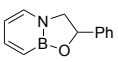
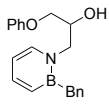
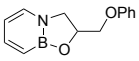
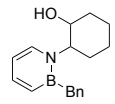
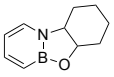
Scheme 5. Synthesis of *C6*-Ethyl BN-Ethylbenzene



We next employed an intramolecular variant of this method to generate BN-dihydrobenzofurans, which serve as BN/CC isosteres of the dihydrobenzofuran moiety found in a variety of natural products and drugs[24] and as potential precursors to BN-benzofurans. To the best of our knowledge there are no examples of BN-isosteres of either class of compounds. The synthesis of BN-dihydrobenzofurans involved a two-step process: a deprotonation/epoxide ring opening sequence starting from azaborine **7** followed by the copper catalyzed boron oxidation reaction which resulted in cyclization (Table 4). Six BN-dihydrobenzofuran isosteres were produced in good yield over two steps with this method including the parent compound **36**, demonstrating the potential for this method to be used to generate a library of BN-dihydrobenzofurans by varying the substitution on the epoxide reaction partner.

Table 4. Synthesis of BN-dihydrobenzofurans

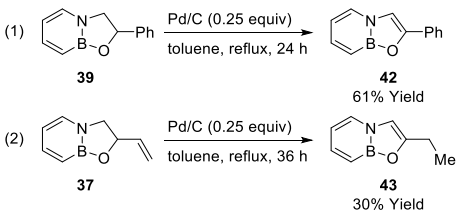


entry	epoxide	ring-opened product (% Yield)[a]	BN-dihydrobenzofuran (% Yield)[a]
1		 **30** 97% Yield	 **36** 81% Yield
2		 **31** 71% Yield	 **37** 77% Yield
3		 **32** 81% Yield	 **38** 88% Yield
4		 **33** 80% Yield	 **39** 79% Yield
5		 **34** 95% Yield	 **40** 84% Yield
6		 **35** 40% Yield	 **41** 26% Yield

[a] Yields shown are isolated yields and are the average of two runs.

Next, we explored the oxidation of several BN-dihydrobenzofurans to the corresponding BN-benzofurans (Scheme 6). Phenyl-substituted **39** was converted to the substituted BN-benzofuran **42** in good yield after refluxing in toluene in the presence of Pd/C for 24 hours; however, only limited success was observed when the same conditions were applied to the other substrates. Vinyl-substituted **37** underwent isomerization rather than oxidation, leading to the isolation of **43** in modest yield. Neither **36** nor **40** was converted to the corresponding BN-benzofurans under these conditions, suggesting that the successful observed reactions may be due to the driving force resulting from extension of π conjugation in **42** and **43**.

Scheme 6. Oxidation to BN-Benzofurans



3. CONCLUSION

We developed two copper-catalyzed reaction systems using either molecular oxygen or DTBP as the stoichiometric oxidant that convert *B*-alkyl or *B*-aryl azaborine substrates to *B*-OR materials that can undergo further functionalization at the boron atom following the transformation. Both reactions are assisted by the presence of a copper salt as an additive, but both reactions still take place without the copper, albeit with a significant loss of efficiency. No metal or Lewis acid additive besides copper was able to efficiently promote the reaction, and we determined that a key species involved in the azaborine oxidation was most likely an alkoxy radical. We investigated the mechanistic features of the reactions by designing straightforward experiments and discovering that bibenzyl is formed as a stoichiometric byproduct during the deprotection of *B*-benzyl substrates. The optimized deprotection protocol is highly effective for the removal of benzyl groups from azaborines, presumably because the benzyl radical that is expelled is relatively stabilized compared to other alkyl or aryl radicals. We applied the new method as the key step in the synthesis of *C6*-ethyl BN-ethylbenzene, and in the synthesis of BN-dihydrobenzofurans and BN-benzofurans which represent unexplored classes of heterocycles. This method will be highly useful to chemists carrying out multi-step transformations of azaborines in particular and perhaps boron heteroarenes in general that require removal of carbon-based boron protecting groups as part of the synthetic plans.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures, spectroscopic data. 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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