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Catalytic Reductions Without External Hydrogen Gas: Broad Scope Hydrogenations with Tetrahydroxydiboron and a Tertiary Amine

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Abstract. Facile reduction of aryl halides with a combination of 5% Pd/C, $B_2(OH)_4$, and 4-methylmorpholine is reported. Aryl bromides, iodides, and chlorides were efficiently reduced. Aryl dihalides containing two different halogen atoms underwent selective reduction: I over Br and Cl, and Br over Cl. Beyond these, aryl triflates were efficiently reduced. This combination was broadly general, effectuating reductions of benzylic halides and ethers, alkenes, alkynes, aldehydes, and azides, as well as for *N*-Cbz deprotection. A cyano group was unaffected, but a nitro group and a ketone underwent reduction to a low extent. When $B_2(OD)_4$ was used for aryl halide reduction, a significant amount of deuteriation occurred. However, H atom incorporation competed and increased in slower reactions. 4-Methylmorpholine was identified as a possible source of H atoms in this, but a combination of only 4-methylmorpholine and Pd/C did not result in reduction. Hydrogen gas has been observed to form with this reagent combination. Experiments aimed at understanding the chemistry led to the proposal of a plausible mechanism and to the identification of *N*,*N*-bis(methyl-d_3)pyridine-4-amine (DMAP-d_6) and $B_2(OD)_4$ as an effective combination f. full aromatic deuteriation.

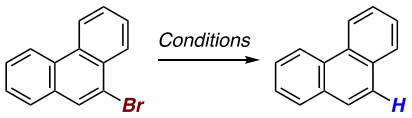
Keywords: reduction; diboron; tetrahydroxydiboron; hydrogenation; deuteriation

Introduction

Diboron compounds, known for over 90 years,[1] have emerged from being chemical curiosities to powerful reagents in organic synthesis.[2,3] Among reactions that do not involve substrate borylation, reductions by diboron reagents are rising in importance. The possibility for reducing amine *N*-oxides by bis(pinacolato)diboron $(pinB)_2$ and bis(catecholato)diboron $(catB)_2$ was demonstrated in 2002 with two pyridine *N*-oxides and 4-methylmorpholine-*N*-oxide.[4] Since then, $(pinB)_2$ has been used to reduce N–O bonds in O^6-(benzotriazol-1-yl)purine nucleosides, leading to C-6 benzotriazol-1-yl nucleoside analogues,[5] and *N*-hydroxyphthalimides.[6] $(PinB)_2$ and $(catB)_2$ are broadly applicable for the reduction of amine *N*-oxides and the former is suitable for reduction under aqueous conditions as well.[7] Subsequently, tetrahydroxydiboron ($B_2(OH)_4$) has featured as a powerful reductant of pyridine *N*-oxides,[8] for converting 1-hydroxy-1*H*-benzotriazoles to 1*H*-benzotriazoles under mild conditions,[9] and recently, in the regiospecific *N*-arylation of benzotriazoles.[10] Whereas these reactions rely on B–B to B–O–B bond conversion, a different type of reduction was reported in 2016, involving $B_2(OH)_4$, Pd/C, and H_2O.[11] Here, hydrogen atoms for the reduction of C=C and C≡C arose from water. Subsequently, $B_2(OH)_4$ and H_2O were used in metal-free reductions of quinolines and quinazolines,[12] and in the reduction step of cyclization-reductive Heck reactions.[13]

The combination of $(pinB)_2$ and H_2O has been the focus of several reduction protocols. In the presence of $Pd(OAc)_2$, quinolines, quinoxalines, and

Table 1. Evaluation of conditions for the reduction of 9-bromophenanthrene to phenanthrene.



Entry	"Pd" (mol %)	$B_2(OH)_4$ (equiv.)	Additive (equiv.)	Conditions	Result[a]
1[b]	5% Pd/C (5)	1.1	H_2O (5)	CH_2Cl_2, rt, 20 h	Inc[c]
2[b]	5% Pd/C (5)	1.1	H_2O (5)	1,2-DCE, 50 °C, 18 h, then 80 °C, 72 h	Inc[c]
3[b]	5% Pd/C (5)	2.2	H_2O (5)	1,2-DCE, 80 °C, 18 h	Inc[c]
4[b]	5% Pd/C (5)	1.1 × 2	pyrrolidine (5 × 2)	1,2-DCE, 50 °C, 24 h, then 50 °C, 20 h	*98%*
5[d]	$Pd_2(dba)_3$ (5)	3.0	H_2O (10)	1,2-DCE, 50 °C, 19 h, then 100 °C, 72 h	–[e]
6[d]	$Pd(OAc)_2$ (5)	3.0	H_2O (10)	1,2-DCE, 50 °C, 22 h	–[e]
7[d]	$Pd(OAc)_2$ (5)	3.0	H_2O (10)	1,2-DCE, Cs_2CO_3 (2.5 equiv.), 50 °C, 19 h, then 100 °C, 72 h	–[e]
8[d]	5% Pd/C (5)	2.2	pyrrolidine (5)	1,2-DCE, 50 °C, 1.5 h	*98%*
9[f]	5% Pd/C (5)	2.2	pyrrolidine (10)	1,2-DCE, 50 °C, 1.5 h	*94%*[g]
10[f]	5% Pd/C (5)	2.2	pyrrolidine (5)	1,2-DCE, 50 °C, 1.5 h	*100%*
11[f]	5% Pd/C (5)	2.2	H_2O (10)	1,2-DCE, 50 °C, 24 h	Inc[c]
12[f]	5% Pd/C (5)	0	pyrrolidine (5)	1,2-DCE, 50 °C, 22 h	NR[h]
13[f]	5% Pd/C (5)	2.2	none	1,2-DCE, 50 °C, 24 h	NR[h]
14[f]	none	2.2	pyrrolidine (5)	1,2-DCE, 50 °C, 24 h	–[e]

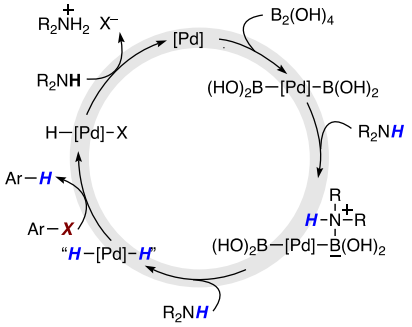
[a] Yield reported is of purified phenanthrene from reactions where little or no 9-bromophenanthrene remained.
[b] Reaction was conducted with 0.6 mmol of 9-bromophenanthrene at a concentration of 0.3 M in the solvent.
[c] Inc = incomplete reaction, a significant amount of 9-bromophenanthrene remained.
[d] Reaction was conducted with 0.2 mmol of 9-bromophenanthrene at a concentration of 0.1 M in 1,2-DCE.
[e] A trace amount of phenanthrene was observed.
[f] Reaction was conducted with 0.2 mmol of 9-bromophenanthrene at a concentration of 0.3 M in 1,2-DCE.
[g] A trace amount of 9-bromophenanthrene remained.
[h] NR = no reaction was observed.

imidazo[2,1*a*]pyridines were reduced (with or without added base),[14] and imidazo[2,1*a*]pyridines with added PCy_3.[15] Aldehydes and ketones were reduced in the presence of DBU, without $Pd(OAc)_2$,[16] but with $Pd(OAc)_2$ and Cs_2CO_3 a quinoline and a pyridine underwent ring reduction, and benzonitrile was reduced to benzylamine.[16] With $CuBr/Cs_2CO_3$, enones and ynones underwent *β*-borylation with $(pinB)_2$ followed by protiodeboronation to give the reduction products.[17,18] Similarly, a borylation/protiodeboronation pathway with $CuBr/Xantphos/Cs_2CO_3$ has been utilized for the reduction of benzofuranyl ketones.[19]

In these reactions, whenever an aromatic halogen atom was present, it remained unaffected. Notably, under the olefin-reducing conditions,[11] an aryl chloride was not reduced, although partial reduction of a bromide, azide, and a nitro group were observed (with partial conversion of substrates).[11] A number of well-established as well as recent methods are available for the reduction of aryl halides.[20–22] However, we were interested in assessing whether aryl halide reduction could be accomplished with a diboron reagent and, if successful, we wished to evaluate the reduction of other functionalities. Such a method would dispense with a need for external, stored hydrogen gas.

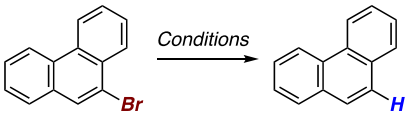
Results and Discussion

Our initial hypothesis (Scheme 1) was that use of a secondary amine could likely result in a strong N–B bond with the boron, after the oxidative addition. Thus, a significantly weakened N–H bond could facilitate formation of a "Pd-H" species, which could reduce an aryl halide. Presence of excess amine could then regenerate Pd(0). On the basis of this rationale,



Scheme 1. An initially proposed mechanism for the reduction of aryl halides to arenes.

Table 2. Influence of other nitrogen-containing additives on the reduction of 9-bromophenanthrene to phenanthrene.[a]



Entry	"Pd" (mol %)	Solvent, additive	Temperature, time	Result[b]
1	5% Pd/C (5)	1,2-DCE, *NH_3*[c]	50 °C, 1 h	*100%*
2	5% Pd/C (5)	1,2-DCE, *Et_3N*	50 °C, 1.5 h	*92%*
3	5% Pd/C (5)	1,2-DCE, *iPr_2NEt*	50 °C, 24 h	*64%*[d]
4	5% Pd/C (5)	1,2-DCE, *PhNHMe*	50 °C, 24 h	–[e]
5	5% Pd/C (5)	1,2-DCE, *4-methylmorpholine*	50 °C, 1 h	*99%*
6	5% Pd/C (5)	1,2-DCE, *1-methylpyrrolidine*	50 °C, 1 h	*98%*
7	5% Pd/C (5)	THF, *4-methylmorpholine*	50 °C, 6.5 h	*74%*[d]
8	5% Pd/C (5)	MeCN, *4-methylmorpholine*	50 °C, 6.5 h	*97%*
9	5% Pd/C (5)	THF, *none*	50 °C, 5 h	–[e]
10	5% Pd/C (5)	MeCN, *none*	50 °C, 5 h	–[e]
11	5% Pd/C (5)	$C_6H_5CH_3$, *4-methylmorpholine*	50 °C, 3.5 h	*99%*
12	5% Pd/C (5)	C_6H_6, *4-methylmorpholine*	50 °C, 30 h	*97%*
13	$Pd(OAc)_2$ (5)	1,2-DCE, *4-methylmorpholine*	50 °C, 21 h	Inc[d]
14	$Pd_2(dba)_3$ (2.5)	1,2-DCE, *4-methylmorpholine*	50 °C, 21 h	Inc[d]
15	none	1,2-DCE, *4-methylmorpholine*	50 °C, 2 h, 5 h, and then 21 h	NR[g]

[a] Reactions were conducted with 0.2 mmol of 9-bromophenanthrene at a concentration of 0.3 M in the solvent, with 2.2 equiv. of $B_2(OH)_4$, and 5 equiv. of the additive.
[b] Yield reported is of purified phenanthrene from reactions where little or no 9-bromophenanthrene remained.
[c] 7 M NH_3 in MeOH was used.
[d] Inc = incomplete reaction.
[e] A trace amount of phenanthrene was observed.
[f] A trace amount of 9-bromophenanthrene remained.
[g] NR = no reaction was observed.

evaluations commenced on 9-bromophenanthrene (a selection is shown in Table 1). The $B_2(OH)_4$ used for these reactions was analyzed on the basis of the ^1H integration values and known chemical shifts.[23] It became immediately evident that the combination of Pd/C, $B_2(OH)_4$, and H_2O, which efficiently reduced olefins and alkynes,[11] was ineffective here (entries 1–3). However, as hypothesized, Pd/C and pyrrolidine led to reduction, but 2 aliquots of$B_2(OH)_4$ and pyrrolidine were needed to attain a complete reaction (entry 4). $Pd_2(dba)_3/H_2O$ and $Pd(OAc)_2/H_2O$ were ineffective (entries 5–7). Further optimizations (entries 8–10) showed 2.2 equiv. of $B_2(OH)_4$ and 5 equiv. of pyrrolidine to be optimal. Doubling the amount of pyrrolidine appeared to lead to a slightly incomplete reaction (entry 9), and even on a lower scale water was less effective (entry 11). Absence of $B_2(OH)_4$, or pyrrolidine, or Pd/C led to practically no reaction (entries 12–14).

Other amines were then evaluated for the reduction of 9-bromophenanthrene (Table 2). NH_3 in MeOH gave a rapid reaction and bubbling was observed (likely evolution of H_2 gas, entry 1). Here, NH_3 and/or MeOH could be a source of hydrogen as was the case with H_2O. More interestingly though, reduction also occurred with tertiary amines Et_3N and iPr_2NEt, but the latter was less efficient (entries 2 and 3). By contrast, *N*-methylaniline was ineffective (entry 4). In this connection, partial reduction of diphenylacetylene with Lindlar catalyst and Et_3N has been shown (71% substrate consumption).[11] Remarkably, 4-methylmorpholine and 1-methylpyrrolidine gave rapid reactions, and proved to be slightly better than Et_3N (entries 5 and 6). Between the two, the cheaper 4-methylmorpholine was selected for further evaluations. Between THF and MeCN, the latter was a better solvent, but 1,2-DCE was superior (entry 5 versus entries 7 and 8).

In THF and MeCN only a trace of product was observed in the absence of an amine (entries 9 and 10). By comparison, 1,1-diphenylethylene was reported to undergo reduction with $B_2(OH)_4$ with variable efficiency in THF in the absence of H_2O.[11] A reaction in toluene was satisfactory (entry 11) but slightly slower than that in 1,2-DCE, and a reaction in benzene was very slow (entry 12). Whereas $Pd(OAc)_2$ and $Pd_2(dba)_3$ were ineffective in combination with water, much better but incomplete conversions were observed with 4-methylmorpholine (entries 13 and 14). Under otherwise comparable conditions, $(pinB)_2$ in place of $B_2(OH)_4$ led to only a trace amount of phenanthrene over 55 h. However, with $(catB)_2$, a 72% yield of phenanthrene was obtained after 24 h

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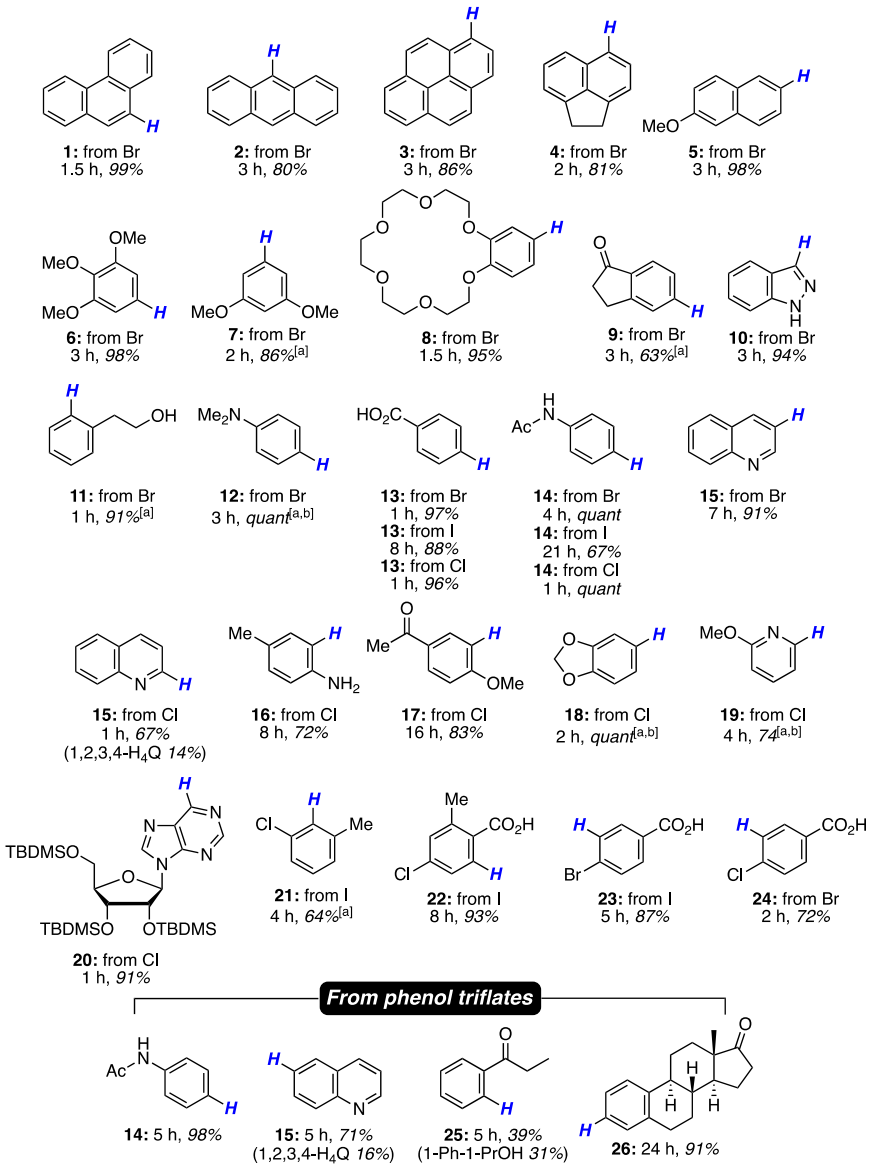


Figure 1. Products from the reduction of aryl halides and triflates, reaction times, and yields. The locations of the halogen atom or triflate in the precursors are the positions occupied by the hydrogen atoms shown in blue in the products. [a] Product is potentially volatile. [b] Yield was assessed using CH_2Br_2 as an internal ^1H NMR standard.

(ca. 80% conversion). To test whether H_3BO_3, present in $B_2(OH)_4$, was responsible for the reduction, 2.2 equiv. of H_3BO_3 was evaluated but it led to no reaction over 24 h. Thus, it is safe to surmise that $B_2(OH)_4$, its dimer, and possibly the trace amount of trimer are involved in this reduction. The amount of 4-methylmorpholine necessary for the reduction was assessed and with 1 and 2 equiv., reductions were only ca. 50% complete. At 3 equiv. the reduction reached completion within 7 h, at 4 equiv. the reaction time was a shorter 80 min, and at 5 equiv. the reaction was complete within 1 h (product yield was 99% in these three cases and incomplete reactions were observed with <3 equiv. of 4-methylmorpholine).

Twenty-nine halogenated substrates were selected for further analysis and because an aryl chloride was not reduced under previously reported conditions,[11] the outcomes with chloro substrates were of particular interest. In addition to aryl bromides and chlorides, some aryl iodides and mixed aryl dihalides were also studied. The results from the reductions of these substrates using 2.2 equiv. of $B_2(OH)_4$ and 5 equiv. of 4-methylmorpholine, in 1,2-DCE at 50 °C are shown in Figure 1. Insofar as possible, isolated product yields are reported, although product volatility may have contributed to lowered yields in some cases. In instances where product isolation was precluded due to volatility, yields were estimated by ^1H NMR analysis of the crude reaction mixtures using CH_2Br_2 (δ = 4.93 ppm in $CDCl_3$) as an internal standard.

Products **1**–**12** were all obtained in good to excellent isolated yields. Notably, the bromophenyl crown ether and 3-bromoindazole were reduced smoothly, giving **8** and **10**, respectively. *N*,*N*-

Dimethylaniline (**12**) was obtained quantitatively (as assessed by ^{1}H NMR). Reduction of all three *p*-halo benzoic acids proceeded well to yield benzoic acid (**13**), except that a longer reaction time was needed for reduction of the iodo precursor. Similarly, *p*-halo acetanilides also underwent smooth reduction to acetanilide (**14**), with the iodo analogue reacting slower. These conditions did not cause reduction of *p*-fluoroacetanilide and this substrate could not be reduced with Pd/C and NH_3 in MeOH or with $(cod)_2Ni$ and 4-methylmorpholine. 3-Bromoquinoline underwent reduction to quinoline (**15**) in a high yield and no ring reduction was observed. In contrast to this, 2-chloroquinoline underwent reduction to yield quinoline (**15**) and 1,2,3,4-tetrahydroquinoline (1,2,3,4-H_4Q, 14% yield). *p*-Toluidine (**16**), *p*-methoxyacetophenone (**17**), 1,3-benzodioxole (**18**), and 2-methoxypyridine (**19**) were obtained by reduction of the respective aryl chlorides. Notably, a keto group was not affected and neither was the pyridine ring. A chloro nucleoside derivative underwent efficient, uncomplicated reduction to the protected nebularine **20**.[24] The reactions of mixed halo arenes proved interesting. Two chloro-iodo arenes underwent selective C–I bond reduction, resulting in products **21** and **22**. The reaction of a bromo-iodo arene also proceeded well, selectively producing **23**. Reduction of a 3-bromo-4-chlorobenzoic acid returned *p*-chlorobenzoic acid (**24**) in good yield, with about 7% of benzoic acid being formed. In some reactions, a small amount (≈ 5–7%) of biaryl formation was observed (please see the Supporting Information for details).

Interestingly, phenol triflates were also reduced (Figure 1). Previously, phenol triflates have been reduced with a combination of a Pd catalyst, phosphine ligand, and an amine (with or without an acid additive), with formate often serving as a source of hydrogen atoms.[25–28] Under the conditions described here, the triflate derivative of 4-acetaminophen[29] was reduced in high yield to acetanilide (**14**). By comparison to the easy reducibility of this triflate, the tosylate and mesylate derivatives underwent reduction in only 5% and 22% yields, respectively (as assessed by ^{1}H NMR). 6-Hydroxyquinoline triflate[30] underwent reduction to quinoline (**15**) in good yield, accompanied by some ring reduction (1,2,3,4-H_4Q, 16% yield), an outcome comparable to that from 2-chloroquinoline (Figure 1). *o*-Hydroxypropiophenone triflate[31] underwent reduction to propiophenone (**25**), accompanied by over reduction to 1-phenyl-1-propanol (1-Ph-1-PrOH, 31% yield). The extent of the carbonyl reduction in this case could be due to the proximity of the two reducible functionalities. The steroidal estrone triflate[32] also underwent reduction in high yield to the deoxygenated analog **26**.[33] These combined results show the facile reducibility of the C–OTf bond.

In order to ascertain the broader utility of these reduction conditions, other functionalities were tested (Figure 2). In this experimentation, some substrates required a modified stoichiometry (4.4 equiv.) of $B_2(OH)_4$ and this is indicated in Figure 2. 1-Chloromethyl and 2-bromomethylnaphthalene were reduced to the corresponding methylnaphthalenes, **27** and **28**, respectively. Interestingly, 2-(phenoxymethyl)naphthalene[34] was also reduced to 2-methylnaphthalene (**28**) in a high yield, comparable to 2-bromomethylnaphthalene. Because this result represented benzylic hydrogenolysis of an ether, yielding the hydrocarbon, debenzylation of 2-benzyloxypyridine and 4-benzyloxyquinazoline[35] were evaluated. These reactions returned excellent yields of 2-pyridone (2-hydroxypyridine, **29**) and 4-quinazolinone (**30**), respectively. On the basis of these debenzylation reactions, cleavage of the Cbz-protection from amines was attempted. 1-Naphthylamine (**31**) was obtained smoothly from benzyl naphthalen-1-ylcarbamate.[36] Next, debenzylation of the *N*-Cbz derivative of (*R*)-1-(1-naphthyl)ethylamine[37] was evaluated. This reaction was complete within 24 h. However, in the ^{1}H NMR spectrum of the crude material, the C*H* (quartet) and the C*H*$_3$ (doublet) were slightly downfield shifted as compared to the authentic product (Figure 1 in the Supporting Information). This could be due to the formation of an amine-boron complex from a relatively basic alkyl amine. Stirring the crude product with ethylenediamine, followed by purification resulted in chemical shifts that exactly matched that of the authentic material (evaluated at identical concentrations, Figure 1 in the Supporting Information). In contrast to these results, debenzylation was not observed under the previously-described olefin-reducing conditions involving H_2O.[11]

Reduction of *trans*-cinnamyl alcohol to 3-phenyl 1-propanol (**33**), *trans*-stilbene to 1,2-diphenylethane (**34**), and 4-aminostyrene to 4-ethylaniline (**35**) proceeded smoothly. The trisubstituted olefin in (*β*)-citronellol was reduced to yield (±)-3,7-dimethyloctan-1-ol (**36**) in a good yield. Reduction of cinnamyl acetate[38] was studied to assess whether only olefin reduction or complete reduction occurred. With 2.2 equiv. of $B_2(OH)_4$, a small amount of 1-phenyl-1-propene was visible in the ^{1}H NMR spectrum of the reaction mixture. However, use of 4.4 equiv. of $B_2(OH)_4$ led to full reduction, yielding propyl benzene (**37**). Next, the reduction of 3-phenyl-2-propyn-1-ol was assessed, where use of 4.4 equiv. of $B_2(OH)_4$ and 10 equiv. of 4-methylmorpholine gave 3-phenyl-1-propanol (**33**) reasonably efficiently (use of 5 equiv. of 4-methylmorpholine gave a comparable outcome). Along similar lines, 1-ethyl-2,4,5-trimethylbenzene (**38**) was obtained from 1-ethynyl-2,4,5-trimethylbenzene with 4.4 equiv. of $B_2(OH)_4$ and 5 equiv. of 4-methylmorpholine (again, use of 10 equiv. of 4-methylmorpholine gave a similar yield). 1-Naphthaldehyde, 1-pyrenecarboxaldehyde, 3,4,5-trimethoxybenzaldehyde, 4-cyanobenzaldehyde, quinoline-6-carbaldehyde, and 2-

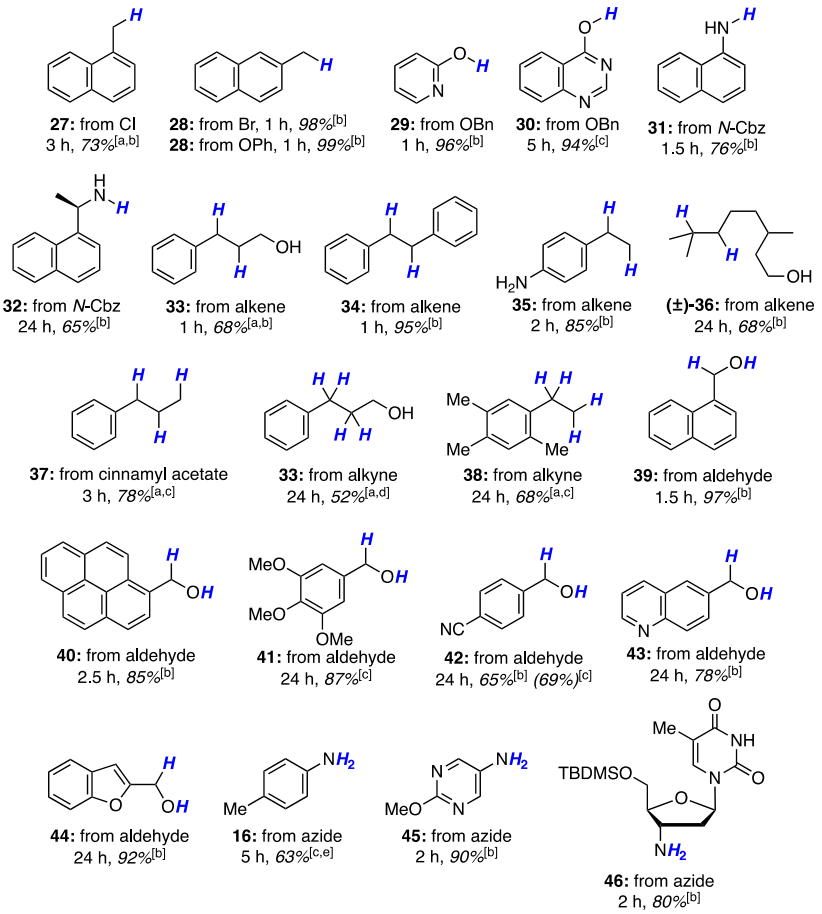


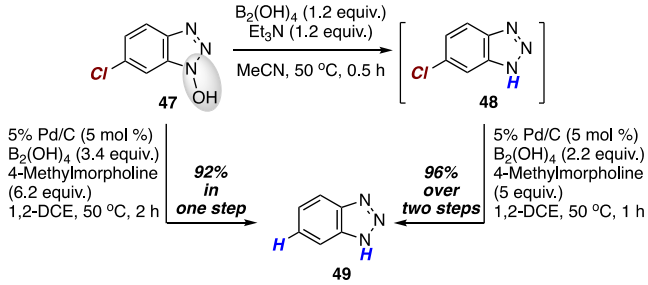
Figure 2. Reduction of benzylic halides, benzylic ethers, a Cbz derivative, alkenes, an allyl acetate, alkynes, aldehydes, and azides. [a] Product is potentially volatile. [b] Reaction was conducted with 2.2 equiv. of $B_2(OH)_4$ and 5 equiv. of 4 methylmorpholine. [c] Reaction was conducted with 4.4 equiv. of $B_2(OH)_4$ and 5 equiv. of 4-methylmorpholine. [d] Reaction was conducted with 4.4 equiv. of $B_2(OH)_4$ and 10 equiv. of 4-methylmorpholine. [e] Product was prone to sublimation under reduced pressure.

benzofurancarboxaldehyde all underwent reduction to the corresponding alcohols (**39**–**44**). In the case of 3,4,5-trimethoxybenzaldehyde, 4.4 equiv. of $B_2(OH)_4$ was used in order to attain complete conversion. The slow reduction in this case may be due to the mesomeric effect of the *p*-methoxy group. As a note, in the reduction of 3'-chloro-4'-methoxyacetophenone (Figure 1), the keto group was not reduced, in contrast to the 12% reduction of 1-acetonaphthone (*vide infra*). Finally, three azides were tested. Among these, 4-tolylazide required 4.4 equiv. of $B_2(OH)_4$ for complete reduction to 4-toluidine (**16**). On the other hand, 5-azido-2-methoxypyrimidine[39] and 5'-*O*-TBDMS-protected 3'-azido-3'-deoxythymidine were smoothly reduced to the corresponding amino derivatives **45** and **46**[40] with 2.2 equiv. of $B_2(OH)_4$. In contrast to the deprotection of benzyl (*R*)-(1-(naphthalen-1-yl)ethyl)carbamate where amine-boron complexation likely occurred, this did not seem to occur in the reduction of TBDMS-protected 3'-azido-3'-deoxythymidine, Cbz cleavage from the aryl amine, and reduction of the aryl azides. The ^{1}H NMR data of **46** was consistent with the literature data.[40]

The reducibility of other functional groups was assessed. In contrast to the reduction of 1-pyrenecarboxyaldehyde, 1-cyanopyrene was not reduced (24 h, 50 °C), but 6-nitroindole gave a 22% yield of the amine (24 h, 50 °C, 50% of starting material was recovered). Aryl nitro groups have previously been reduced with $(pinB)_2$/*t*-BuOK/iPrOH at 110 °C, $(pinB)_2$/KF/EtOH at 100 °C, Pd on C/$B_2(OH)_4$ and water at 50 °C, or $Cu(OAc)_2$/$B_2(OH)_4$/MeCN at 80 °C, without reduction of a C-halogen bond where tested.[41–44] 1-Acetonaphthone gave a 12% yield of the alcohol (24 h, 50 °C, 87% of starting material was recovered). In order to learn whether 1,2-DCE underwent reduction under the conditions, 3-phenyl-1-chloropropane was subjected to the reaction conditions. 1-Phenylpropane was formed to an extent of 15% in 24 h (by ^{1}H NMR).

The previously reported reduction of 6-chloro-1-hydroxy-1*H*-benzotriazole (**47**) presented an interesting case study for two experiments (Scheme

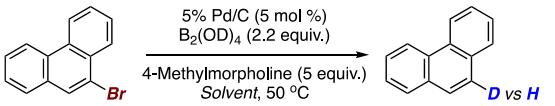
2).[9] In one experiment, the N–OH group was first reduced with $B_2(OH)_4$ and Et_3N in MeCN at 50 °C to yield intermediate **48**,[9] followed by reduction of the C–Cl bond with $B_2(OH)_4$ and 4-methylmorpholine in the same reaction vessel, to give benzotriazole (**49**). The second experiment was a one-step reduction of **47** to **49** using Pd/C, $B_2(OH_4)$, and 4-methylmorpholine. Both reactions proceeded well and, notably, reduction of the N–O and C–Cl bonds could be accomplished within 2 h by the one-step method.



Scheme 2. Two-step, one-pot, and a one-step reduction of 6-chloro-1-hydroxy-1*H*-benzotriazole.

The source of hydrogen atoms for the reduction was then probed. For this $B_2(OD)_4$ was prepared as previously described.[11] Its ^1H NMR spectrum (in DMSO-d_6) indicated the absence of protons (attempts to conduct H/D exchange on $B_2(OH)_4$ by multiple treatments with CD_3OD and evaporations indicated a slow and incomplete exchange). Six reactions were conducted with $B_2(OD)_4$ (Table 3). Under the optimized conditions, 68% incorporation of D was observed and this improved to 76% upon washing the Pd/C with CH_3OH, 1,2-DCE, and drying under vacuum (entries 1 and 2). This was not significantly altered when the washing was performed with CD_3OD (entry 3). A reaction in 1,2-DCE-d_4 (entry 4) indicated that the hydrogen atoms did not arise from the solvent. Reactions in benzene and benzene-d_6 were essentially comparable but the extents of hydrogen atom incorporation were much greater than in 1,2-DCE (entries 5 and 6).

Table 3. Reduction of 9-bromophenanthrene with $B_2(OD)_4$, 4-methylmorpholine, and 5% Pd on carbon.[a]



Entry	Solvent	Time	Deuteriation [%]
1	1,2-DCE	1.5 h	68
2	1,2-DCE	1.5 h[b]	76
3	1,2-DCE	1.5 h[c]	73
4	1,2-DCE-d_4	1.5 h	70
5	C_6H_6	30 h	48
6	C_6D_6	30 h	46

[a] Reactions were conducted with 0.2 mmol of 9-bromophenanthrene at a concentration of 0.3 M in the solvent.

[b] Pd/C was washed thrice with CH_3OH, once with 1,2-DCE, and vacuum dried.

[c] Pd/C was washed thrice with CD_3OD, once with 1,2-DCE, and vacuum dried.

NMR experiments did not readily provide insight to mechanistic details. However, from the data in Table 3, key information is discernible. Deuterium atoms from $B_2(OD)_4$ and by inference, hydrogen atoms from $B_2(OH)_4$, become available for the reduction, but competitive hydrogen atom incorporation is observed during deuteriation. In comparing entries 1 and 4, no deuterium atoms (and by inference, hydrogen atoms) seem to be obtained from the solvent. By exclusion, this leaves 4-methylmorpholine as a source of hydrogen atoms. The unavailability/high cost of deuterated alkyl amines precluded evaluations with one. When reactions were relatively fast (entries 1–4) the proportion of deuteriation was greater as compared to the much slower reactions in C_6H_6 or C_6D_6, where nearly equal amounts of H and D were incorporated (entries 1–4 *versus* entries 5 and 6). Thus, D/H exchange appears possible along the reaction path, which could then account for the greater incorporation of H in the slower reactions. A reaction using $B_2(OH)_4$ and 4-methylmorpholine in 1,2-DCE, *with 2 equiv. of* D_2O, resulted in only a 12% incorporation of D. This shows that H atom incorporation from adventitious moisture is not a likely cause for the observed results *and* that H/D exchange with the diboron is a slow process. These results collectively point to the possibility that a significant proportion, but not all of the hydrogen atoms for the reduction may be obtained from the diboron reagent. From a reaction of 9-bromophenanthrene under the optimized conditions, the headspace of the mixture was analyzed by ^1H NMR. This showed a resonance at $\delta = 4.62$ ppm (in $CDCl_3$), the reported value for H_2 in $CDCl_3$,[45] and GC analysis also indicated the formation of H_2 (Figures 2 and 3 in the Supporting Information).

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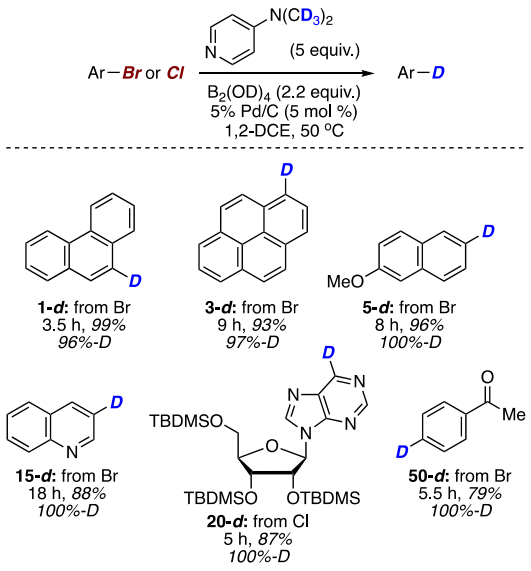
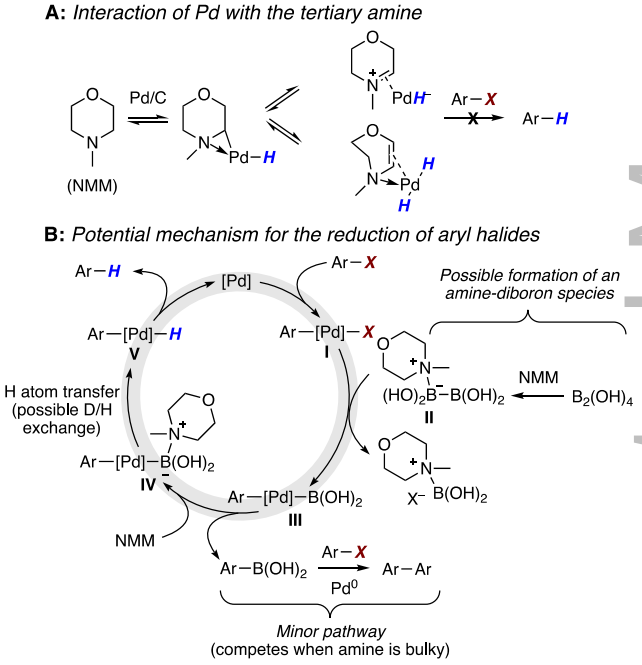
Deuteriation then became a focus and because appropriate deuteriated alkyl amines are not readily available, assessments were conducted with amines that can be easily deuteriated. *N*,*N*-Dimethylaniline, 1,2,2,6,6-pentamethylpiperidine, and 4-*N*,*N*-dimethylaminopyridine (DMAP) were evaluated for the reduction of 9-bromophenanthrene (Table 4 in the Supporting Information). Nearly complete reduction occurred with *N*,*N*-dimethylaniline, but over 68 h. A surprising result was obtained with 1,2,2,6,6-pentamethylpiperidine where, in addition to reduction, nearly 50% of 9,9'-biphenanthrene was obtained (in 10 h), a result apparently connected to the mechanism (*vide infra*). DMAP gave a promising 99% yield of phenanthene (**1**) within 3.5 h (no reduction occurred without $B_2(OH)_4$). Being a slower reaction (3.5 h *versus* 1.5 h with 4-methylmorpholine), only 52% deuteriation occurred when $B_2(OD)_4$ and DMAP were employed. With *N*,*N*-bis(methyl-d_3)pyridine-4-amine (see the Supporting Information for its preparation) and $B_2(OD)_4$, six substrates were deuteriated (Scheme 3) in high yields and with high deuterium incorporation. These results support the hypothesis that hydrogen atoms from the diboron and the amine become available for the reductions.



Scheme 3. Six deuteriated products that were synthesized using DMAP-d_6. The locations of the halogen atom in the precursors are the positions occupied by the deuterium atoms shown in blue in the products.

On the basis of the foregoing, it is reasonable to anticipate that amine-Pd^0 interactions alone, producing "Pd–H" intermediates, could lead to the reduction of aryl halides. However, in 1,2-DCE at 50 °C, no reduction occurred with 5% Pd/C and 4-methylmorpholine without $B_2(OH)_4$. Also, reported reductions involving amines generally require higher reaction temperatures. Thus, imine-PdH and enamine-PdH_2 species (Scheme 4**A**) are likely not direct reductants but could contribute to a D/H exchange process in the deuteriation. Lewis acid-base interaction of the boron and amine is inadequate, because a mixture of Pd/C, BF_3•Et_2O, and 4-methylmorpholine was ineffective. Thus, the combination of $B_2(OH)_4$, 4-methylmorpholine, and Pd/C appears uniquely capable of reduction.

Mechanistically, amines interact with Pd^{II} and Pd^0, and are reductants of the former.[46–49] Of relevance here, Pd^0 is known to react with amines containing α- and β-hydrogen atoms, to form hydrido-Pd species, *via* imine and enamine formation.[46,47] In deuteriation experiments, greater incorporation of D was observed at the α-position in tertiary amines.[47] *n*-Bu_3N, 1,2,2,6,6-pentamethylpiperidine, 1,4-dioxane, Me_2NH formed from DMF at temperatures >120 °C, and Et_3N are known reductants in reactions catalyzed by Pd complexes.[26,28,50–52] Of particular note, Pd/C and Et_3N have been used for reducing α,β-unsaturated carbonyls and a nitrile (at 120–200 °C) but, under the conditions, a vinyl chloride was not reduced at 140 °C.[53]



Scheme 4. Potential imine-Pd and enamine-Pd complexes that can be formed (**A**) and a plausible mechanism for the reduction of aryl halides and triflates (**B**).

A possible mechanism (Scheme 4**B**) involves oxidative-addition complex **I** reacting with an amine-boron complex **II**, resulting in **III**. From **III**, one possibility is the direct formation of Ar–Pd–H (**V**) by transfer of "H" from the B–OH bond to the Pd center, with expulsion of metaborate (O=B–OH). Ar–Pd–H (**V**) could then lead to the reduced product. Whereas metaborate formation has been postulated in a

reduction of nitroarenes by $B_2(OH)_4$,[44] in the absence of evidence for its formation, this remains speculative. As an alternate, a second amine can bind at the boron center in **III** to give species **IV** from which formation of **V** can lead to reduction. It is currently unclear how H/D from the diboron and/or amine becomes attached to the Pd center but this can explain the partial deuteriation observed with $B_2(OD)_4$/4-methylmorpholine.

With DMAP-d_6/$B_2(OD)_4$ complete deuteriation occurred. The use of 1,2,2,6,6-pentamethylpiperidine is interesting in this context, where the reaction took 10 h to reach completion, possibly due to the steric bulk of this amine. This factor could slow the conversion of **III** to **IV** as well, promoting greater Miyaura borylation,[54] and increasing the secondary cross coupling leading to the biaryl. Thus, the minor amounts of biaryl observed with 4-methylmorpholine could be due to this process, which becomes amplified when 1,2,2,6,6-pentamethylpiperidine is used. "PdH_2" as a reductant can also be formed as in Scheme 1. The hydrogen gas produced could account for the reduction of carbon-carbon unsaturation and azide functionality, as well as cleavage of benzyl and Cbz groups. Transfer hydrogenation[55,56] could account for aldehyde reduction.

In the context of amine-diboron interactions, synthesis of the sp^3–sp^3 diboron species 2,2'-bi(1,3,6,2-dioxazaborocane) was recently reported.[57] This entity produces H_2 with water and has been used for reducing alkenes and for the partial hydrogenation of alkynes.[57] This is reminiscent of the reduction of amine *N*-oxides by tetraethyldiborane, forming H_2 in the process.[58] Evidence suggests that 2,2'-bi(1,3,6,2-dioxazaborocane) may form a borohydride and a borinic acid that recombine, to produce H_2.[57] Because a borohydride could be formed from 2,2'-bi(1,3,6,2-dioxazaborocane), aldehydes *and* ketones were reduced.[57] By comparison to this reaction, the present work demonstrates a uniquely new reductive capability of $B_2(OH)_4$, in combination with Pd/C and a tertiary amine.

Conclusion

In summary, we set out to assess whether reduction of aryl halides by $B_2(OH)_4$ is achievable. We found that the combination of 5% Pd/C, $B_2(OH)_4$, and 4-methylmorpholine in 1,2-DCE can effectuate reductions of aryl and benzylic halides, aryl triflates, benzylic ethers, alkenes, alkynes, azides, and deprotection of the *N*-Cbz functionality, under mild conditions. 4-Methylmorpholine is a cheap, volatile reagent that does not complicate compound purifications. Formation of H_2 gas from the combination of $B_2(OH)_4$, 4-methylmorpholine and 5%Pd/C was observed by ^1H NMR and GC analysis. Experiments with $B_2(OD)_4$ indicated significant availability of deuterium atoms from the diboron reagent, but deuteriation was not exclusive, and 4-methylmorpholine was identified as a possible source of hydrogen atoms. The extent of deuteriation decreased with longer reaction times, indicating possible D/H exchange along the reaction path. On the basis of the mechanistic knowledge gained, aryl deuteriation was achieved using *N*,*N*-bis(methyl-d_3)pyridine-4-amine in combination with $B_2(OD)_4$. The unusual reactivities of diboron reagents constitute an emerging field and this work, by comparison to others, shows how subtle variations of conditions can result in markedly different outcomes.

Experimental Section

Please see the Supporting Information for general experimental considerations.

General method for the reduction [9-bromophenanthrene → phenanthrene (1)]

To a solution of 9-bromophenanthrene (257.1 mg, 1 mmol) in DCE (3.3 mL) in a 8 mL vial equipped with a micro stir bar, was added $B_2(OH)_4$ (197.2 mg, 2.2 mmol), 5% Pd/C (106.5 mg, 0.05 mmol), and 4-methylmorpholine (NMM, 0.55 mL, 5 mmol). The vial was tightly capped and the reaction mixture was stirred at 50 °C for 1.5 h. The mixture was then filtered through Celite and the residue was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure. Purification on a silica column packed in hexanes and eluted with hexanes gave 177.5 mg (99% yield) of compound **1** as a white solid. (In some reactions small amounts of the known 9,9'-biphenanthrene was isolated.[59])

Similar conditions, with any noted variations, were used for the other transformations.

General method for the reduction of benzoic acids

To a solution of the halo benzoic acid (1 mmol) in DCE (3.3 mL) in a 8 mL vial equipped with a micro stir bar, were added $B_2(OH)_4$ (197.2 mg, 2.2 mmol), 5% Pd/C (106.5 mg, 0.05 mmol), and 4-methylmorpholine (NMM, 0.55 mL, 5 mmol). The vial was tightly capped and the reaction mixture was stirred at 50 °C until full conversion of the starting material. The mixture was then filtered through Celite and the residue was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure. To the crude product (a sticky solid) 1 M HCl (10 mL) was added. The white precipitate was filtered and dried under vacuum to give the corresponding pure product.

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FULL PAPER

Catalytic Reductions Without External Hydrogen Gas: Broad Scope Hydrogenations with Tetrahydroxydiboron and a Tertiary Amine

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