# Pd-Catalyzed Transfer Hydrogenation of Alkenes Using Tetrahydroxydiboron as the Sole Hydrogen Donor

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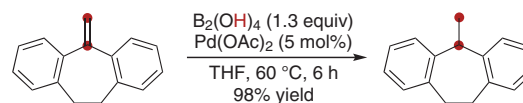
- $B_2(OH)_4$ is the sole H donor
- efficient D incorporation using $B_2(OD)_4$ is demonstrated
- a variety of stabilized & unstabilized C=C's readily reduced

Abstract Tetrahydroxydiboron-mediated catalytic transfer hydrogenations have typically involved co-additives that, like tetrahydroxydiboron itself, are H atom donors. Herein we report an alkene transfer hydrogenation method with tetrahydroxydiboron as the sole source of H atoms. The reaction uses $Pd(OAc)_2$ as a convenient putative colloid precatalyst, and cyclic monoethers are competent solvents. Highly efficient alkene deuteration is demonstrated using tetradeuteroxydiboron.

Key words tetrahydroxydiboron, transfer hydrogenation, palladium catalysis, alkene reduction, deuterium, catalytic hydrogenation
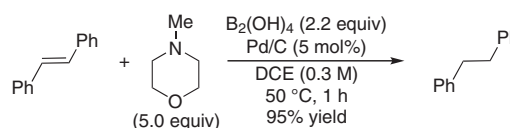
Transition-metal-catalyzed hydrogenation is one of the most important reactions in synthetic chemistry and is widely used and studied in both industry and academia.[1] Catalytic hydrogenation is often accomplished by direct application of H_2 gas, which is formally 'byproductless', but safety and environmental concerns arise due to H_2 production, transportation, storage, and handling. To avoid these and other inconveniences associated with the direct application of H_2, transfer hydrogenation (TH) allows in situ generation of stoichiometric H_2, with the expense of stoichiometric byproduct generation from the transfer reagent.[2] Longstanding transfer reagents include formic acid,[3] primary alcohols,[4] ammonia borane,[5] and silanes.[6]

Since 2016, we and others have developed methods for transition-metal-catalyzed transfer hydrogenation and hydrogenolysis reactions of a variety of organic functional groups using tetrahydroxydiboron-mediated processes with water or alcohols serving as H atom codonors.[7] Among
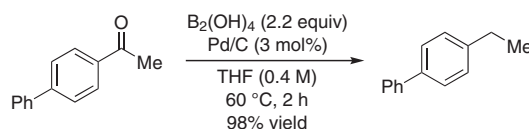
the common diborane reagents,[8] $B_2(OH)_4$ is the most atom-economical and is being used industrially for the transition-metal-catalyzed synthesis of aryl boronic acids.[9] More recently there have been examples of transfer hydrogenation or hydrogenolysis using $B_2(OH)_4$ without a polar protic additive. For example, in 2020, Lakshman and coworkers reported the Pd/C-catalyzed reduction of aryl halides, aldehydes, alkenes, and alkynes using $B_2(OH)_4$ and 4-methylmorpholine (Scheme 1A).[10]

Interestingly, 4-methylmorpholine served as a formally aprotic codonor of H atoms. More recently, our lab described a Pd/C-catalyzed transfer deoxygenation of benzylic
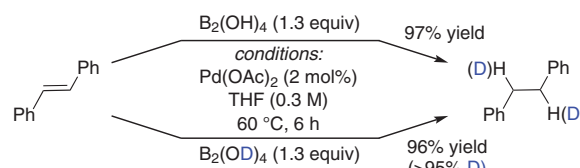

Scheme 1 Relevant examples of catalytic transfer reductions mediated by tetrahydroxydiboron

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ketones using $B_2(OH)_4$ as the sole H-atom source in THF.[11] Herein, we report a Pd-catalyzed $B_2(OH)_4$-mediated alkene transfer hydrogenation method using $Pd(OAc)_2$ as a precatalyst and no H-atom codonor (Scheme 1C).

The optimized conditions[12] are similar to those we recently published for the ketone deoxygenation.[11] In either case, common aprotic diboron reagents B_2pin_2 and B_2cat_2 afford no substrate conversion (see the Supporting Information for details). We evaluated a variety of polar solvents and found that amongst ethers, cyclic monoethers (Scheme 2, first row) are suitable for the reduction of *trans*-stilbene, whereas 1,4-dioxane and acyclic ethers (row 2) are less so. This may be due to the attenuated polarity of 1,4-dioxane and cyclic monoethers compared to the cyclic monoethers, which, beyond their ability to stabilize the putative metaboric acid byproduct,[11,13] may limit their ability to dissolve $B_2(OH)_4$. Acetonitrile and triethylamine (row 3) also exhibit some efficacy, while 1,2-dichloroethane, toluene, and DMSO yield no product.[12]
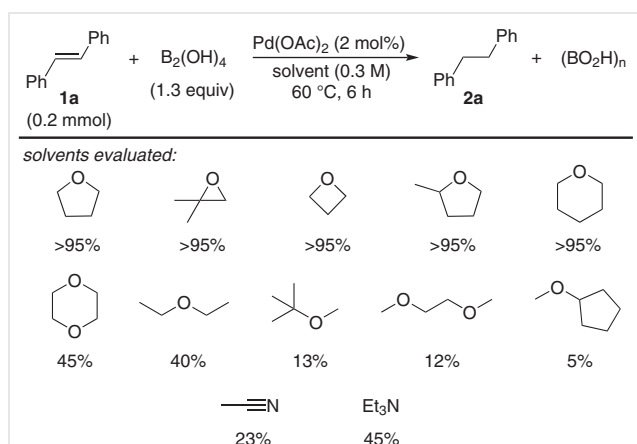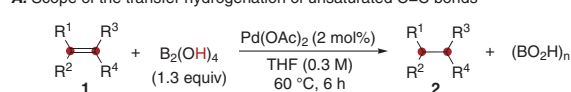

Scheme 2 Solvent effects on hydrogenation yield. Yields of **2a** determined by ^{1}H NMR analysis of the crude reaction mixture compared to 1,3,5-trimethoxybenzene as an internal standard.
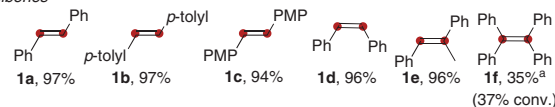
We then investigated the scope of the transfer hydrogenation of various alkenes as substrates using the optimized conditions and THF as solvent (Scheme 3A). Di- and trisubstituted stilbenes **1a**–**e** are efficiently reduced, regardless of alkene geometry (cf., **1a** and **1d**). In contrast, tetraphenylethylene (**1f**) reacts incompletely even after heating for a full day. Interestingly the water-mediated variant, performed at ambient temperature in dichloromethane, rapidly reduces tetraphenylethylene at room temperature.[7a] A variety of styrenes (**1g**–**o**) were evaluated and all afford yields greater than 90%. Furthermore, ethyl cinnamate (**1p**) undergoes efficient reduction of its α,β-unsaturation, as does chalcone (**1q**), whereas benzylideneacetone (**1r**), featuring an enolizable ketone, affords a low C=C reduction yield of 32% due to observed competing carbonyl reduction. Excitingly, dutasteride (**1s**), a prescription active pharma-

ceutical ingredient for the treatment of benign prostatic hyperplasia, undergoes selective reduction of its α,β-unsaturation position, albeit at a slow rate. We also evaluated the reduction of a few isolated alkenes using compounds **1t**–**x**. Oleic acid (**1t**), a Boc-protected dihydropyrrole (**1u**), and three terminal alkenes (**1v**, **1w**, and **1x**) were all efficiently hydrogenated. Diphenylacetylene (**3**) was also subjected to similar reduction conditions although with twice the amount of additive and catalyst (Scheme 3B). The major product is *cis*-stilbene (**1d**, 43% yield), with *trans*-stilbene (**1a**) observed in 16% yield, and just 5% of bibenzyl (**2a**) produced.

Scheme 3 Substrate scope of the transfer hydrogenation. These reactions were conducted on 0.5 mmol scale. Unless otherwise noted, full conversion was observed and reported yields are of isolated products (PMP = *p*-methoxyphenyl). [a] Reaction time was 24 hours. [b] Due to product volatility, ^{1}H NMR yield is reported (compared to 1,3,5-trimethoxybenzene as an internal standard). [c] ^{1}H NMR yield compared to 1,3,5-trimethoxybenzene as an internal standard. [d] Conducted on 0.2 mmol scale.

As shown in Scheme 4 below, we performed additional experiments on *trans*-stilbene (**1a**) to assess the fidelity of deuterium isotope incorporation, evaluated a deuterium kinetic isotope effect, and determined the influence of mercury on the catalysis. Excitingly, Scheme 4A shows that *trans*-stilbene incorporates deuterium from $B_2(OD)_4$ virtually quantitatively. This is exciting because deuterium-enriched compounds are valuable medicinally[14,15] and as probes of organic reaction mechanisms.[16] This also validates the hypothesis that the diboron reagent is the sole source of hydrogen atoms. A competition kinetic isotope effect (KIE) study[17,18] was performed using equimolar amounts of $B_2(OH)_4$ and $B_2(OD)_4$ (Scheme 4B), resulting in a KIE of 2.3 as determined from the ratio of products **1a**/**1a-d_2**. Although the transfer of the H atom to form the putative palladium hydride is not likely the rate-determining step, this result informs about the formation of the putative palladium hydride, and especially interesting compared to the competition KIE previously reported for the B_2cat_2-mediated reduction of diphenylacetylene using equimolar H_2O and D_2O in dichloromethane, which resulted in a competition KIE of 5.6.[7a]

Scheme 4 Applications and mechanistic studies on *trans*-stilbene. These reactions were conducted on 0.2 mmol scale. Isolated yields are reported and conversion matched the yield unless otherwise noted. [a] Mercury was added after eight minutes to allow for catalyst induction. [b] Yield and % conv. determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Lastly, a mercury drop test was performed (Scheme 4C). Near-complete conversion is achieved when mercury is added following an eight-minute induction period.[19] In contrast, the yield and conversion decrease slightly (92% each) if mercury is added immediately, suggesting some inhibition of catalyst induction from $Pd(OAc)_2$ (not shown).

Considering the putative colloidal ligandless nature of this reaction, the outcome of these mercury drop experiments – perhaps limited in their utility – is difficult to interpret.

In conclusion, we have developed a method for the Pd-catalyzed transfer hydrogenation of a variety of unsaturated C–C bonds mediated by $B_2(OH)_4$ using $Pd(OAc)_2$ as a convenient precatalyst,[20,21] and quantitative alkene deuteration has been demonstrated using $B_2(OD)_4$.[22]

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2367-6943.

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(20) **General Transfer Hydrogenation Procedure**
An oven-dried one-dram disposable borosilicate vial is charged with a magnetic stir bar, 58.3 mg of tetrahydroxydiboron (0.65 mmol, 1.3 equiv), 2.3 mg of Pd(OAc)$_2$ (0.01 mmol, 0.02 equiv), and substrate if solid (0.5 mmol, 1.0 equiv). The vial is capped and purged with argon or nitrogen gas, then charged with 1.7 mL of degassed anhydrous THF and heated to 60 °C for 6 h with stirring at 600 rpm. After cooling to ambient temperature, the solution is filtered through a plug of silica gel and rinsed with dichloromethane.

(21) **Characterization Data of Representative Product 2a**
Yield (0.5 mmol scale): 88 mg (97%), colorless solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.29–7.25 (m, 4 H), 7.21–7.16 (m, 6 H), 2.92 (s, 4 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 142.1, 128.6, 128.4, 126.0, 38.0.

(22) A version of this manuscript was deposited on ChemRxiv prior to review: Yaghoubi, M.; Reyes, I. C.; Stokes, B. J. *ChemRxiv* **2024**, preprint DOI: 10.26434/chemrxiv-2024-k2qdm.