

Tetrahydroxydiboron-Mediated Palladium-Catalyzed Transfer Hydrogenation and Deuteriation of Alkenes and Alkynes Using Water as the Stoichiometric H or D Atom Donor

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S Supporting Information

ABSTRACT: There are few examples of catalytic transfer hydrogenations of simple alkenes and alkynes that use water as a stoichiometric H or D atom donor. We have found that diboron reagents efficiently mediate the transfer of H or D atoms from water directly onto unsaturated C–C bonds using a palladium catalyst. This reaction is conducted on a broad variety of alkenes and alkynes at ambient temperature, and boric acid is the sole byproduct. Mechanistic experiments suggest that this reaction is made possible by a hydrogen atom transfer from water that generates a Pd–hydride intermediate. Importantly, complete deuterium incorporation from stoichiometric D₂O has also been achieved.

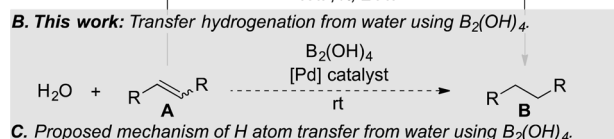
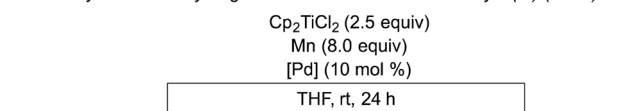
The catalytic hydrogenation of alkenes or alkynes is most often executed in batches by direct application of hydrogen gas. Alternatively, transfer hydrogenation (TH) appeals to many bench chemists because it does not require the use of a flammable gas. A wide variety of H or D atom donors are available for use in both homo- and heterogeneous catalytic TH reactions,¹ but there are few examples of TH reactions that use water stoichiometrically to hydrogenate an unsaturated carbon–carbon bond² despite the safety and cost benefits associated with the use of H₂O and D₂O. While stoichiometric TH of unactivated alkenes and alkynes using H₂O could be broadly useful for reductions, the transfer deuteriation (TD) of alkenes and alkynes using D₂O is of special interest because deuterium-labeled small molecules are useful for the study of synthetic mechanistic pathways,³ for pharmacokinetic studies toward drug discovery,⁴ and for preparing LC-MS internal standards.⁵

The only method we are aware of that uses a near-stoichiometric amount of water as the putative H atom donor relies on a single electron transfer from titanocene chloride to activate the O–H bond for metal hydride generation (Scheme 1A).² This reaction suffers from inconsistent yields and incomplete deuterium incorporation from D₂O. We envisioned developing a complementary approach to metal hydride generation from water by harnessing the versatility of B₂X₄ reagents, which can serve as both a transition metal oxidant and as a Lewis acid to engage water.

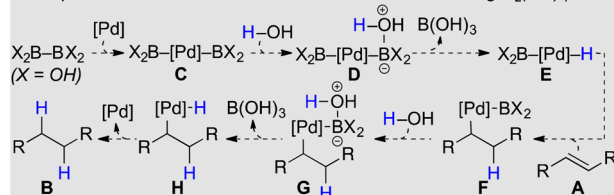
Tetrahydroxydiboron, which is infrequently used for non-borylative purposes,⁶ was envisioned as the ideal diboron

Scheme 1. Use of Water as the H Atom Donor in Catalytic Transfer Hydrogenations of Alkenes

A. Homolytic transfer hydrogenation from water mediated by Ti(III) (ref. 2).



C. Proposed mechanism of H atom transfer from water using B₂(OH)₄.

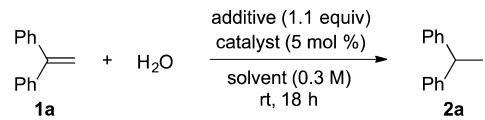


reagent to transfer H atoms from water across unsaturated carbon–carbon bonds (Scheme 1B). Mechanistically, we hypothesized that, following oxidative addition to give C,⁷ water could coordinate to one boron atom to give adduct D (Scheme 1C). Then, H atom transfer could liberate boric acid to afford Pd-hydride E.⁸ Migratory insertion of an unsaturated substrate, such as A, could afford Pd-alkyl intermediate F, which could coordinate another equivalent of water (G) and generate Pd-hydride H following another hydrogen atom transfer event. Reductive elimination from H could generate the second C–H bond and afford B. Below, we describe the successful development of this concept into an efficient hydrogenation and deuteriation reaction that avoids the necessity of H₂ or D₂ gas and reduces a wide variety of alkenes and alkynes to alkanes quantitatively at ambient temperature.⁹

We discovered that untreated palladium on carbon (Pd/C) could quantitatively transfer hydrogen atoms from water to 1,1-diphenylethylene 1a at ambient temperature in dichloromethane in the presence of tetrahydroxydiboron and just a slight excess (2.1 equivalents total, with 1 equivalent required per B atom) of water (Table 1, entry 1). This result suggests that H₂ gas is not being generated by B₂(OH)₄ hydrolysis *in*

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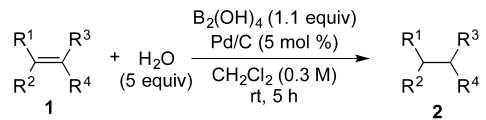
Table 1. Reaction Optimization^a


entry	catalyst	additive	solvent	H ₂ O (equiv)	yield (%) ^b of 2a
1	Pd/C	B ₂ (OH) ₄	DCM	2.1	>95
2	Pd/C	B ₂ (OH) ₄	DCM	0	0
3	Pd/C	B ₂ (OH) ₄	MeOH	0	65
4	Pd/C	B ₂ (OH) ₄	THF	0	50
5 ^c	Pd/C	B ₂ (OH) ₄	DCM	5	0
6	Pd(PPh ₃) ₄	B ₂ (OH) ₄	DCM	5	0
7 ^d	Pd/C	B ₂ (OH) ₄	DCM	5	10
8	Pd(OAc) ₂	B ₂ (OH) ₄	DCM	5	>95
9	Pd/C	B ₂ cat ₂	DCM	5	>95
10	Pd/C	B ₂ pin ₂	DCM	5	<5

^aThese reactions employed untreated catalysts unless otherwise noted and were conducted on 0.2 mmol scale. In all cases, the substrate conversion matched the yield. ^bDetermined by ¹H NMR analysis of reaction mixtures upon filtration using 1,3,5-trimethoxybenzene as an internal standard. ^cReduced Pd/C was used in this experiment. ^dThis reaction was conducted in the presence of 145 equivalents of Hg per Pd.

situ, as H₂ would be likely to escape from solution and lead to low yield if this were the case. Alternatively, B₂(OH)₄ hydrolysis would lead to the intermediate H–B(OH)₂, which could potentially hydroborate the alkene to give alkyl boronic acids, but alkyl boronic acids do not proteodeboronate under our reaction conditions.¹⁰ No background hydrogenation occurred in dichloromethane in the absence of water (entry 2), whereas hydrogenation did occur in anhydrous MeOH (entry 3) and anhydrous THF (entry 4) in the absence of added water. Turning our attention to the catalyst itself, we found that a prereduced form of Pd/C did not afford a detectable amount of product (Table 1, entry 5), suggesting that the reaction may be catalyzed by metal nanoparticles.¹¹ The use of Pd(PPh₃)₄ as catalyst also resulted in no substrate conversion, further implicating catalytically active Pd nanoparticles, which would be poisoned by phosphines (entry 6).⁷ As a final piece of evidence in support of the nanoparticulate nature of the catalyst, a mercury drop experiment was performed and resulted in a significant decrease in the conversion of 1a (entry 7).¹² In addition to untreated Pd/C, Pd(OAc)₂ was also observed to catalyze the reaction (entry 8). Pt/C and Rh/C are also effective catalysts.¹³ As our final piece of optimization, we probed the influence of the electronic nature of the diboron reagent and found that the arene-stabilized bis(catecholato)diboron variant functioned as efficiently as tetrahydroxydiboron (Table 1, entry 9). In contrast, bis(pinacolato)diboron afforded only trace amounts of product (entry 10), underscoring the importance of the electronic nature of the diboron reagent.^{6a,14}

With optimized conditions in hand, we began exploring the scope of alkenes that could be hydrogenated with water, starting with terminal nonstyrenyl alkenes (Table 2, 1b–1f). This group was hydrogenated in high yield in each case and includes octene (1b), as well as substrates bearing oxygen-containing functional groups, such as primary alcohols (1c), benzyl ethers (1d), esters (1e), and α,β-unsaturated ketones (1f). Disubstituted cyclic alkenes were readily hydrogenated, including aliphatic (1g and 1h) and heterocyclic substrates (1i

Table 2. Scope of The Hydrogenation of Alkenes^a


entry	substrate	yield (%)	conversion (%)
terminal non-styrenyl alkenes			
1b	<i>n</i> -Hex	>95%	
1c	HO-(CH ₂) ₃	>95%	
1d	BnO-(CH ₂) ₃	97%	
1e	EtO ₂ C-CH=CH-CO ₂ Et	91%	
1f	Et-C(=O)-CH=CH ₂	>95%	
cyclic alkenes			
1g	1,2-dimethylcyclopentene	>95%	
1h	1,2-dimethylcyclohexene	>95%	
1i	1,2-dimethylcycloheptene	>95%	
1j	1,2-dimethylcyclooctene	97%	
1k	1-chlorocyclopentene	trace	64% conv.
1l	(+)-terpineol	69%	75:25 trans:cis
acyclic polysubstituted alkenes			
1m	Ph-CH=CH-CO ₂ Et	90%	
1n	Ph-CH=CH-CH ₂ OH	21%	58% conv.
1o	Ph-CH=CH-CH ₂ OBn	90%	93% conv.
1p	Ph-CH=CH-CH ₂ OTIPS	95%	
1q	Ph-CH=CH-Ph	97%	
1r	Ph-CH=CH-Ph	95%	
1s	Ph-CH=CH-t-Bu	95%	
1a	Ph-CH=CH-Ph	92%	
1t	Ph-CH=CH-Me	99%	
1u	Ph-CH=CH-Ph	88%	88% conv.
1v	Me-CH=CH-Me	>95%	
1w	Ph-CH=CH-CO ₂ H	88%	95% conv.
styrenes			
1x	C ₆ H ₅	96%	
1y	<i>p</i> -OMe(C ₆ H ₄)	96%	
1z	<i>p</i> -Cl(C ₆ H ₄)	96%	
1aa	<i>p</i> -CF ₃ (C ₆ H ₄)	93%	
1ab	<i>p</i> -NO ₂ (C ₆ H ₄)	38%	55% conv.
1ac	<i>p</i> -N ₃ (C ₆ H ₄)	6%	77% conv.
1ad	<i>p</i> -Br(C ₆ H ₄)	32%	82% conv.
1ae	<i>m</i> -Br(C ₆ H ₄)	51%	66% conv.
1af	<i>o</i> -Br(C ₆ H ₄)	25%	84% conv.
1ag	C ₆ H ₅ -Br	0%	66% conv.

^aIsolated yields are reported, and starting material was consumed in full, unless otherwise noted. ^bDetermined by ¹H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. ^c60 h reaction of 5.0 mmol of the indicated substrate using 0.5 mol % Pd/C. ^dReaction time was 18 h. ^eH₂O was used as the solvent.

and 1j). In contrast, 1-chlorocyclopentene (1k) afforded only a trace amount of 2k, while (+)-terpineol 1l afforded a reasonable product yield with modest diastereoselectivity favoring the *trans* diastereomer.

Most of the acyclic polysubstituted alkenes that we evaluated (1m–1w) were cleanly converted to product, with the exception of *trans*-cinnamyl alcohol (1n). In this case, aldehyde byproducts predominate, likely due to Pd-induced isomerization.^{13,15} Additionally, during reaction monitoring of *cis*-stilbene 1r, isomerization to *trans*-stilbene 1q was observed, suggesting a reversible H atom addition.¹³ Excellent yields were achieved for trisubstituted (1t and 1w) and even tetrasubstituted (1u and 1v) alkenes. Notably, acetamidocinnamic acid 1w was successfully hydrogenated in 88% yield using H₂O as solvent.

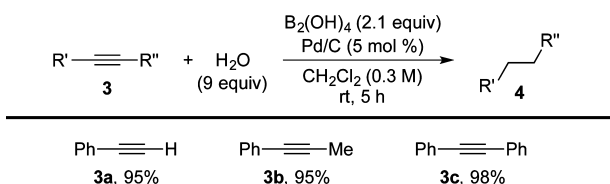
Various styrenes were also readily hydrogenated (1x–1aa), including those bearing electron-donating (1y) and electron-withdrawing (1z and 1aa) groups; no dehalogenation of 1z was observed. In contrast, styrenes bearing functional groups sensitive to reducing conditions, such as a nitro group (1ab), an azide (1ac), and aryl (1ad–1af) and alkenyl (1ag) bromides

afforded low yields of the desired products due to competing functional group reduction, hydrogenolysis, and styrene polymerization.¹⁵ Nonetheless, these examples are instructive in that they show that the reaction conditions can be used to reduce functional groups other than unsaturated C–C bonds.

This reaction is readily executed on 5.0 mmol scale (Table 2, 1a, 1j, and 1q) to afford the corresponding products in excellent yield. These scaled-up reactions were carried out using just 0.5 mol % of catalyst; consequently, these reactions required an extended reaction time (60 hours).

The reaction conditions can also be used to reduce alkynes (Table 3). In these cases, 2.1 equivalents of tetrahydroxydiboron

Table 3. Scope of The Hydrogenation of Alkynes^a

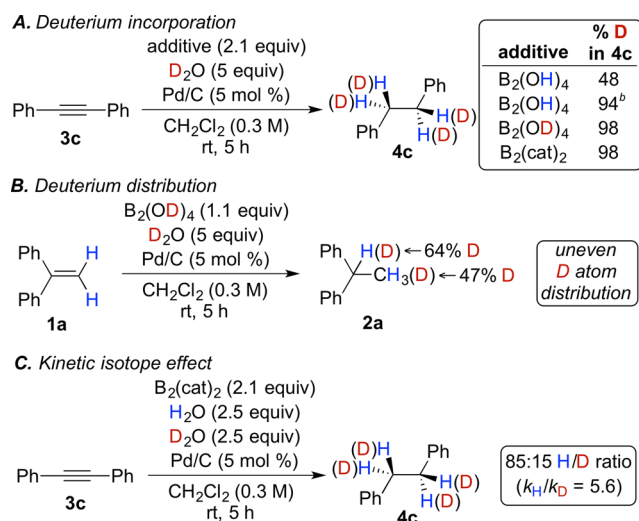


^aIsolated yields are reported, and starting material was consumed in full. Reactions were conducted on 0.6 mmol scale.

are required to fully reduce the alkyne. Simple unactivated alkynes including phenyl acetylene (3a), 1-phenyl-1-propyne (3b), and diphenylacetylene (3c) were nearly quantitatively hydrogenated to the corresponding alkane products.¹⁶

We selected 3c as a model substrate for D atom incorporation from D₂O. Subjection of 3c to our optimized conditions using D₂O instead of H₂O resulted in only 48% deuterium incorporation (Scheme 2A). We ascribe this

Scheme 2. Isotopic Mechanistic Experiments^a



^aComplete substrate conversion occurred in all cases. ^bUsed 50 equivalents of D₂O.

disparity to the exchange of the D atoms of water with the H atoms of tetrahydroxydiboron. By using a substantial excess of D₂O (50 equivalents), 94% D incorporation was observed. To achieve stoichiometric D atom incorporation from D₂O, either B₂(OD)₄ or hydroxyl-free bis(catecholato)diboron are required: 98% D atom incorporation was achieved using just 1.2 equivalents of heavy water per boron atom. These results

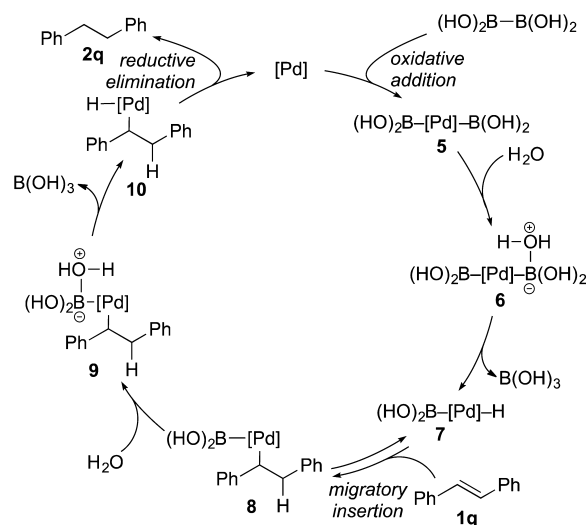
are an improvement upon the 74% D atom incorporation efficiency reported by Oltra and co-workers.²

Having achieved conditions for near-quantitative alkyne deuteration using stoichiometric D₂O, we sought to apply our method to the deuteration of unsaturated C–C bonds comprised of inequivalent carbon atoms. Using 1,1-diphenylethylene 1a as substrate, we observed the expected net incorporation of one deuterium atom per alkyl carbon atom of the starting alkene, but the deuterium atoms were unevenly distributed (Scheme 2B): the benzylic position was only 64% deuterated, while the methyl group was 47% deuterated. Combined with the observed isomerization of 1q described above (Table 2), this suggests that H or D atoms may readily migrate between the benzylic and homobenzylic carbon atoms of 1a.¹⁷

In our third and final study involving deuterium atoms, we employed an equimolar mixture of H₂O and D₂O to probe the existence of a kinetic isotope effect (Scheme 2C). Subjection of 3c to our reaction conditions in the presence of an equimolar mixture of H₂O and D₂O revealed a primary kinetic isotope effect of 5.6 of the reaction. For comparison, the reported catalytic transfer hydrogenation of the dimethyl ester analog of 1e in the presence of an equimolar mixture of H₂O and D₂O using titanocene(III) afforded no deuterated product at all.² Further, a small (<1.5) deuterium isotope effect is observed for both homo- and heterogeneous palladium-catalyzed hydrogenation reactions when using an equimolar mixture of H₂ and D₂ gas.¹⁸

Based on our observations, we propose the following putative catalytic cycle for the hydrogenation of alkenes and alkynes using *trans*-stilbene 1q as a representative alkene (Scheme 3).

Scheme 3. Putative Catalytic Cycle for Hydrogenation of *trans*-Stilbene by Water Using Tetrahydroxydiboron



Initial oxidative addition of the B–B bond to palladium could occur to afford 5. Water could then coordinate to a Lewis acidic boron atom to afford 6. H atom transfer could then furnish palladium hydride 7.⁸ At this point, the alkene could reversibly¹⁹ insert into 7 to give Pd–alkyl 8,²⁰ followed by water coordination and a second H atom transfer to give alkyl–Pd–hydride 10. Intermediate 10 could then undergo reductive elimination to give the hydrogenated product (2q, in this example).

In conclusion, we have discovered a new method that hydrogenates alkenes and alkynes quantitatively at ambient temperature and pressure by stoichiometric atom transfer from H₂O using a diboron additive. We are currently working to better understand the mechanistic intricacies of this process, including the nature of the active catalyst and the identity of the rate-determining step, in order to enable the design of new reactions. We are also investigating new ways to harness this mode of O–H bond weakening for other transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/jacs.6b02132](https://doi.org/10.1021/jacs.6b02132).

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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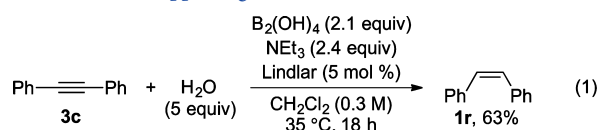
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(16) The use of the Lindlar catalyst for the partial reduction of **3c** resulted in no reaction under the conditions optimized for Pd/C. However, at 35 °C using triethylamine, a 63% NMR yield of *cis*-stilbene **1r** is observed (eq 1). No attempt was made to optimize this reaction. See the [Supporting Information](#) for details.



(17) Deuterium migration was also observed when using Rh/C and Pt/C catalysts. See the [Supporting Information](#) for details.

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(19) A crossover experiment also supports the existence of a reversible step involving C–H bond cleavage. See the [Supporting Information](#) for details.

(20) The subsection of norbornene **1h** to our deuteration conditions results exclusively in *exo* deuteration, implying a *syn* migratory insertion. See the [Supporting Information](#) for experimental details.