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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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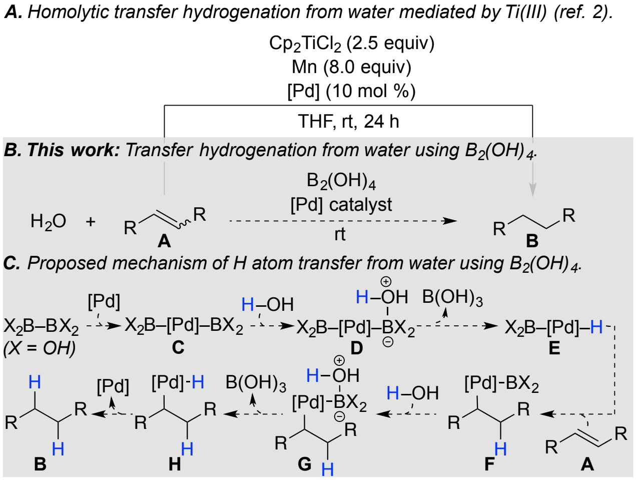
Supporting Information Placeholder

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 rate-determining H atom transfer event that generates a Pd–hydride intermediate. Importantly, complete deuterium incorporation from stoichiometric D_2O 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 bond[2] despite the safety and cost benefits associated with the use of H_2O and D_2O. While stoichiometric TH of unactivated alkenes and alkynes using H_2O could be broadly useful for reductions, the transfer deuteriation (TD) of alkenes and alkynes using D_2O is of special interest because deuterium-labeled small molecules are useful for the study of synthetic mechanistic pathways,[3] for pharmacokinetic studies towards 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 D_2O. We envisioned developing a complementary approach to metal hydride generation from water by harnessing the versatility of B_2X_4 reagents, which can serve as both a transition metal oxidant and as a Lewis acid to engage water.

Scheme 1. The 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).*

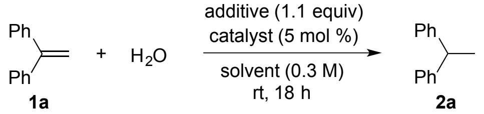
***B. This work:** Transfer hydrogenation from water using $B_2(OH)_4$.*

***C.** Proposed mechanism of H atom transfer from water using $B_2(OH)_4$.*

Tetrahydroxydiboron, which is infrequently used for non-borylative purposes,[6] was envisioned as the ideal diboron 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 H 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 H_2 or D_2 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 one equivalent required per B atom) of water (Table 1, entry 1). This result suggests that H_2 gas is not being generated by $B_2(OH)_4$ hydrolysis *in situ*, as H_2 would be likely to escape from solution and lead to low yield if this were the case. Alternatively, $B_2(OH)_4$ hydrolysis would lead to the intermediate $H–B(OH)_2$, which could potentially hydroborate the alkene to give

Table 1. Reaction Optimization



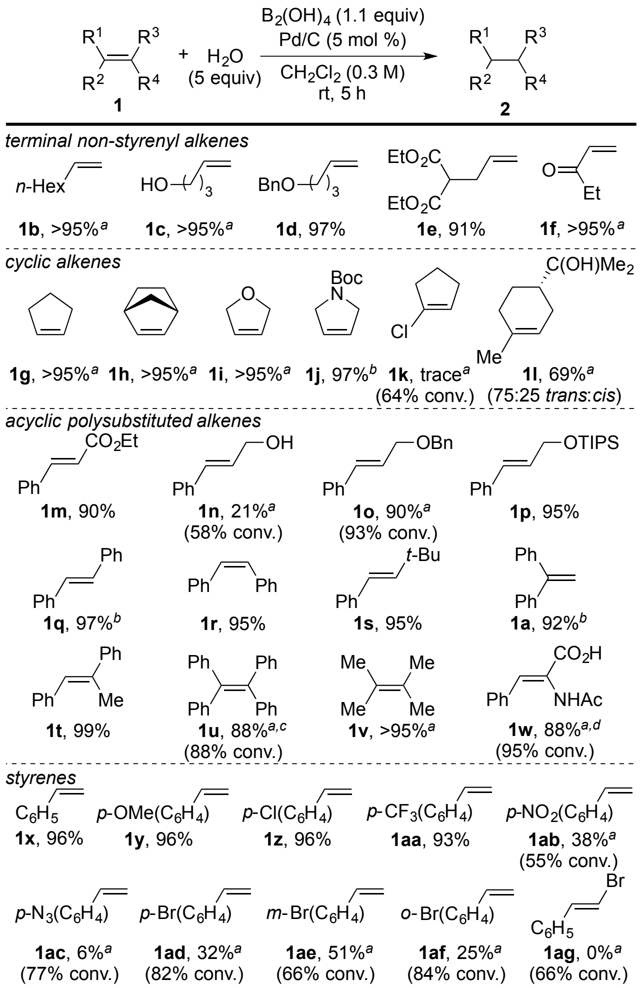
Entry	Catalyst	Additive	Solvent	H_2O (equiv)	Yield (%)[a] of **2a**
1	Pd/C	$B_2(OH)_4$	DCM	2.1	>95
2	Pd/C	$B_2(OH)_4$	DCM	0	0
3	Pd/C	$B_2(OH)_4$	MeOH	0	65
4	Pd/C	$B_2(OH)_4$	THF	0	50
5[b]	Pd/C	$B_2(OH)_4$	DCM	5	0
6	$Pd(PPh_3)_4$	$B_2(OH)_4$	DCM	5	0
7[c]	Pd/C	$B_2(OH)_4$	DCM	5	10
8	$Pd(OAc)_2$	$B_2(OH)_4$	DCM	5	>95
9	Pd/C	B_2cat_2	DCM	5	>95
10	Pd/C	B_2pin_2	DCM	5	<5

These reactions employed untreated catalysts unless otherwise noted, and were conducted on 2.0 mmol scale. In all cases, the substrate conversion matched the yield. [a] Determined by ^{1}H NMR analysis of reaction mixtures upon filtration using 1,3,5-trimethoxybenzene as an internal standard. [b] Reduced Pd/C was used in this experiment. [c] This reaction was conducted in the presence of 145 equivalents of Hg per Pd.

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 $Pd(PPh_3)_4$ 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 effeciently 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 non-styrenyl alkenes (Table 2, **1b**–**1f**). This group was hydrogenated in quantitative 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** and **1j**). In contrast, 1-chlorocyclopetene (**1k**) afforded only a trace amount of **2k**, while (+)-terpineol **1l** afforded reasonable product yield with modest diastereoselectivity favoring the *trans* diastereomer.

Table 2. Scope of The Hydrogenation of Alkenes



Isolated yields are reported, and starting material was consumed in full, unless otherwise noted. [a] Determined by ^{1}H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. [b] 60 hour reaction of 5.0 mmol of the indicated substrate using 0.5 mol % Pd/C. [c] Reaction time was 18 h. [d] H_2O was used as the solvent.

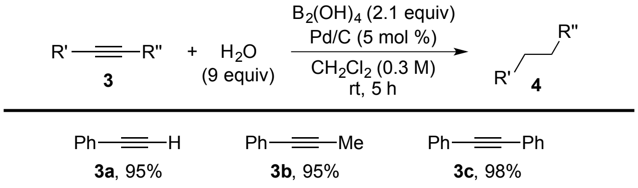
Most of the acyclic polysubstituted alkenes that we evaluated (**1m**–**1w**) were cleanly converted to product, with the exception of *trans*-cinnamyl alcohol (**1n**). In this case, aldehyde byproducts predominate, likely due to Pd-induced isomerization.[13,15] Additionally, during reaction monitoring 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 H_2O 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.[13] 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 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 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]

Table 3. Scope of The Hydrogenation of Alkynes



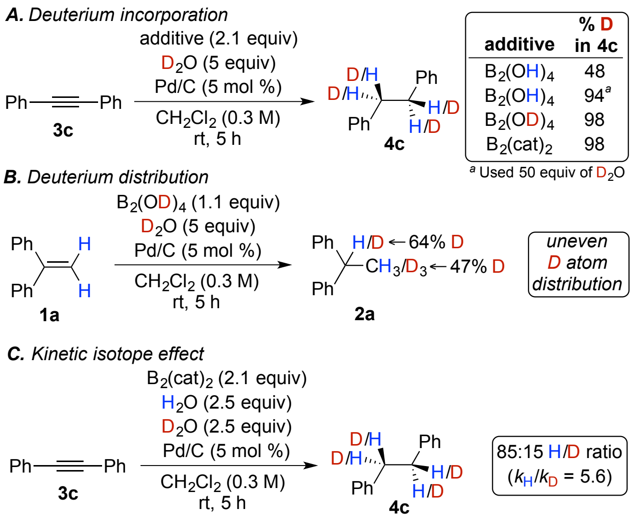
Isolated yields are reported, and starting material was consumed in full. Reactions were conducted on 0.6 mmol scale.

We selected **3c** as a model substrate for D atom incorporation from D_2O. Subjection of **3c** to our optimized conditions using D_2O instead of H_2O resulted in only 48% deuterium incorporation (Scheme 2A). We ascribe this disparity to the exchange of the D atoms of water with the H atoms of tetrahydroxydiboron. By using a substantial excess of D_2O (50 equivalents), 94% D incorporation was observed. To achieve stoichiometric D atom incorporation from D_2O, either $B_2(OD)_4$ or hydroxyl-free bis(catecholato)diboron are required: 98% D atom incorporation was achieved using just 1.2 equivalents of water per boron atom. These results are an improvement upon the 74% D atom incorporation efficiency reported by Oltra and co-workers.[2] The apparent non-quantitative deuterium incorporation could be ascribed to either adventitious water, or the exchange of aromatic H atoms via Pd-π-benzyl isomerization.[17]

Having achieved conditions for near-quantitative alkyne deuteriation using stoichiometric D_2O, we sought to apply our method to the deuteriation 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% deuteriated, while the methyl group was 47% deuteriated. 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**.[18]

In our third and final study involving deuterium atoms, we employed and equimolar mixture of H_2O and D_2O 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 H_2O and D_2O revealed a primary kinetic isotope effect of 5.6, suggesting that H atom bond cleavage occurs in the rate-determining step 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 H_2O and D_2O using titanocene(III) afforded no deuteriated 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 H_2 and D_2 gas.[19]

Scheme 2. Isotopic Mechanistic Experiments (Note: Complete Substrate Conversion Occurred in All Cases)

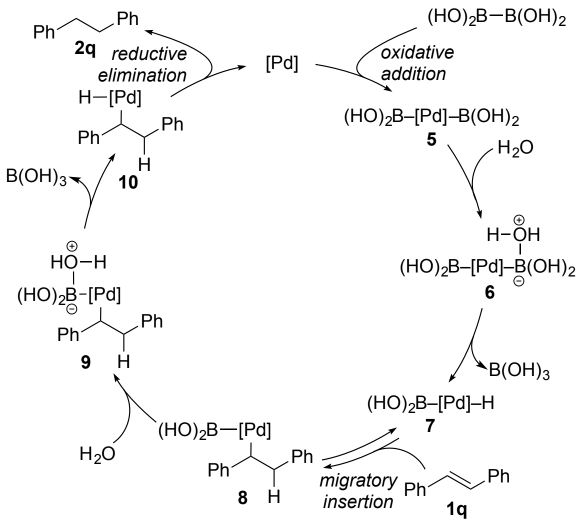


additive	% D in 4c
$B_2(OH)_4$	48
$B_2(OH)_4$	94[a]
$B_2(OD)_4$	98
$B_2(cat)_2$	98

[a] Used 50 equiv of D_2O

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). 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 reversibly[20] insert into **7** to give Pd–alkyl **8**,[21] followed by water coordination and a second H atom

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



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 H_2O 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. Experimental procedures and characterization 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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REFERENCES

(1) (a) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621; (b) Sloan, M. E.; Staubitz, A.; Lee, K.; Manners, I. *Eur. J. Org. Chem.* **2011**, *2011*, 672; (c) Connolly, T.; Wang, Z.; Walker, M. A.; McDonald, I. M.; Peese, K. M. *Org. Lett.* **2014**, *16*, 4444; (d) Paryzek, Z.; Koenig, H.; Tabaczka, B. *Synthesis* **2003**, 2023; (e) Chen, T.; Xiao, J.; Zhou, Y.; Yin, S.; Han, L.-B. *J. Organomet. Chem.* **2014**, *749*, 51; (f) Horn, S.; Albrecht, M. *Chem. Commun.* **2011**, *47*, 8802.

(2) Campaña, A. G.; Estévez, R. E.; Fuentes, N.; Robles, R.; Cuerva, J. M.; Buñuel, E.; Cárdenas, D.; Oltra, J. E. *Org. Lett.* **2007**, *9*, 2195.

(3) For leading references, see: (a) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 7744; (b) Amatore, M.; Gosmini, C.; Périchon, J. *J. Org. Chem.* **2006**, *71*, 6130.

(4) (a) Elmore, C. S. *Annu. Rep. Med. Chem.* **2009**, *44*, 515; (b) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (c) Katsnelson, A. *Nature Med.* **2013**, *19*, 656. (d) Jarman, M.; Poon, G. K.; Rowlands, M. G.; Grimshaw, R. M.; Horton, M. N.; Potter, G. A.; McCague, R. *Carcinogenesis* **1995**, *16*, 683.

(5) For a leading reference, see: Neubert, L.; Michalik, D.; Bähn, S.; Imm, S.; Neumann, H.; Atzrodt, J.; Derdau, V.; Holla, W.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 12239.

(6) (a) Londregan, A.; Piotrowski, D.; Xiao, J. *Synlett* **2013**, *24*, 2695; (b) Pilarski, L. T.; Szabó, K. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 8230; (c) Baber, R. A.; Norman, N. C.; Orpen, a. G.; Rossi, J. *New J. Chem.* **2003**, *27*, 773; (d) Gurram, V.; Akula, H. K.; Garlapati, R.; Pottabathini, N.; Lakshman, M. K. *Adv. Synth. Cat.* **2015**, *357*, 451.

(7) Oxidative additions of diboron reagents to homogeneous Pd catalysts are known, but rare. See: (a) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766. For theoretical investigations, see: (b) Sakaki, S.; Kikuno, T. *Inorg. Chem.* **1997**, *36*, 226; (c) Cui, Q.; Musaev, D. G.; Morokuma, K. *Organomet.* **1998**, *17*, 742.

(8) H atom transfer could occur via σ-bond metathesis. For a nickel-catalyzed example, see: Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* **2001**, *2*, 2688.

(9) The reduction of allylic alcohols has been reported as a side reaction when using $B_2(OH)_4$ to prepare allyl boronic acids: (a) Raducan, M.; Alam, R.; Szabó, K. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 13050. Alkene and alkyne reduction has been achieved using decaborane in methanol: (b) Lee, S. H.; Park, Y. J.; Yoon, C. M. *Tetrahedron Lett.* **2000**, *41*, 887.

(10) Phenethylboronic acid is not consumed in the presence of Pd/C and water. See the Supporting Information for details.

(11) (a) Agostini, G.; Lamberti, C.; Pellegrini, R.; Leofanti, G.; Giannici, F.; Longo, A.; Groppo, E. *ACS Catal.* **2014**, *4*, 187; (b) Raspolli Galletti, A. M.; Bonaccorsi, F.; Calvani, F.; Di Bugno, C. *Cat. Commun.* **2006**, *7*, 896.

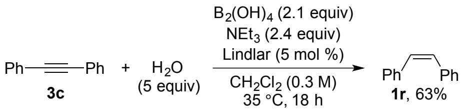
(12) (a) Hintermair, U.; Campos, J.; Brewster, T. P.; Pratt, L. M.; Schley, N. D.; Crabtree, R. H. *ACS Cat.* **2014**, *4*, 99; (b) Gieshoff, T. N.; Villa, M.; Welther, A.; Plois, M.; Chakraborty, U.; Wolf, R.; Jacobi von Wangelin, A. *Green Chem.* **2015**, *17*, 1408; (c) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem* **2003**, *198*, 317.

(13) See the Supporting Information for complete details.

(14) Molander, G. A.; Trice, S. L. J.; Tschaen, B. *Tetrahedron* **2015**, *71*, 5758.

(15) (a) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226; (b) Muzart, J. *Eur. J. Org. Chem.* **2015**, *2015*, 5693.

(16) The use of 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.



(1)

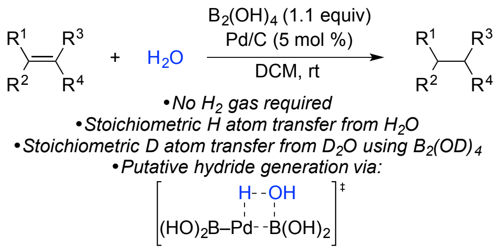
(17) Esaki, H.; Ohtaki, R.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *J. Org. Chem.* **2007**, *72*, 2143.

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

(19) Samuel, B.; Ohrt, W. *Chem. Commun.* **1971**, 1529.

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

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



- *No H_2 gas required*
- *Stoichiometric H atom transfer from H_2O*
- *Stoichiometric D atom transfer from D_2O using $B_2(OD)_4$*
- *Putative hydride generation via:*