

Tetrahydroxydiboron-Mediated Palladium-Catalyzed Deoxygenative Transfer Hydrogenation of Aryl Ketones

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Supporting Information Placeholder

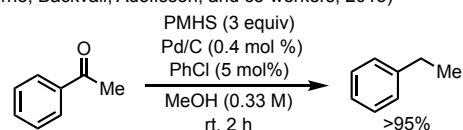
ABSTRACT: We describe a palladium-catalyzed deoxygenative transfer hydrogenation of ketones using $B_2(OH)_4$ as the sole additive. Deuterium labeling experiments using $B_2(OD)_4$ show that the incorporated protons originate exclusively from the diboron reagent. Spectroscopic evidence implicates the intermediacy of a borate ester. A wide array of aromatic ketones can be deoxygenated using this approach.

Reductive deoxygenation is an important process in the biofuels industry and in synthetic organic chemistry.¹ Traditional methods to achieve reductive deoxygenation of ketones using stoichiometric reagents include the Wolff–Kishner, Clemmensen, and Mozingo reductions, which are generally associated with high temperatures, toxic stoichiometric reagents, and strongly acid or basic conditions, all of which limit substrate scope.² Transition metal-catalyzed deoxygenations using H_2 gas involve either high reaction temperature or pressure, specialty non-commercial catalysts, or electrolytic H_2 generation.^{3–12} Alternatively, catalytic transfer deoxygenation of ketones allows for reactions with simple, procedurally safe, and often mild operating conditions. Such transfer deoxygenation methods predominantly employ polymeric silanes as hydrogen atom donors.^{13–16} Notably, Verho, Bäckvall, Adolfsson, and co-workers developed a heterogeneous palladium-catalyzed transfer deoxygenation of ketones at ambient temperature using polymethylhydrosiloxane (PMHS) as the hydride source (Scheme 1A).¹³ Pd-catalyzed systems often require the addition of an acid or acid-generating co-catalyst (in this example, chlorobenzene) to promote the hydrogenolysis of an alcohol intermediate.^{13,14}

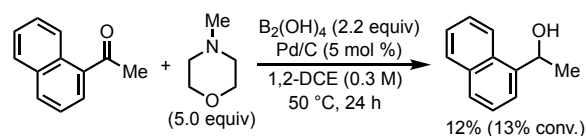
Tetrahydroxydiboron and other diboron(4) reagents have recently emerged as versatile reductants in palladium-catalyzed transfer hydrogenations, with tetrahydroxydiboron being the most atom economical.^{17–24} In 2016 our group disclosed a $B_2(OH)_4$ -mediated Pd-catalyzed transfer hydrogenation of unsaturated C–C bonds wherein added water served as a hydrogen atom co-donor.¹⁹ More recently, Lakshman and co-workers reported a Pd-catalyzed method that utilizes $B_2(OH)_4$ and N-methylmorpholine (NMM) to reduce a variety of functional groups including aryl halides,

Scheme 1. Relevant Examples of Palladium-Catalyzed Transfer Deoxygenations of Ketones

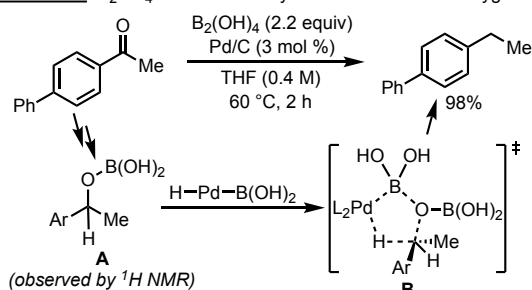
A. Catalytic transfer deoxygenation of ketones in methanol (Verho, Bäckvall, Adolfsson, and co-workers, 2015)¹³



B. Ketones resist $B_2(OH)_4$ -mediated catalytic transfer hydrogenation (Lakshman and co-workers, 2020)²¹



C. **This work:** $B_2(OH)_4$ -mediated catalytic ketone transfer deoxygenation

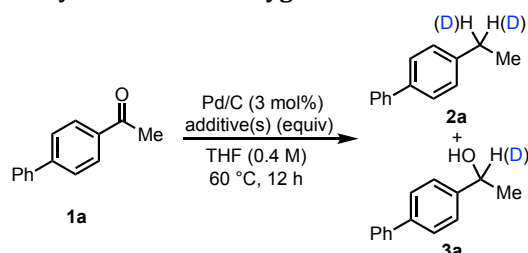


- high atom economy using $B_2(OH)_4$ as discrete (and only) additive
- high fidelity transfer deuteration using $B_2(OD)_4$
- no protic co-mediator and no protic solvent

alkenes, and aldehydes, with aldehydes being semi-reduced to alcohols (ketones were not readily reduced; see Scheme 1B).²¹ To the best of our knowledge, diboron(4)-mediated ketone deoxygenation has never been reported. Herein, we describe a catalytic system for deoxygenation of aromatic ketones using $B_2(OH)_4$ as the sole source of H atoms (Scheme 1C). The C–O bond cleavage of borate ester intermediate A (which is observed by 1H NMR) could proceed via transition state B in a coordinating solvent like THF.

Unreduced palladium on carbon was the best-performing catalyst that we evaluated, and THF the optimal solvent (other solvents led to significantly reduced conversion; see Table S1 in the Supporting Information for complete optimization details). A slight excess of $B_2(OH)_4$ afforded deoxygenated product **2a** and semireduced **3a** in 20% and 54%

Table 1. Probing the Role of the Diboron(4) Mediator in Pd-Catalyzed Ketone Deoxygenations



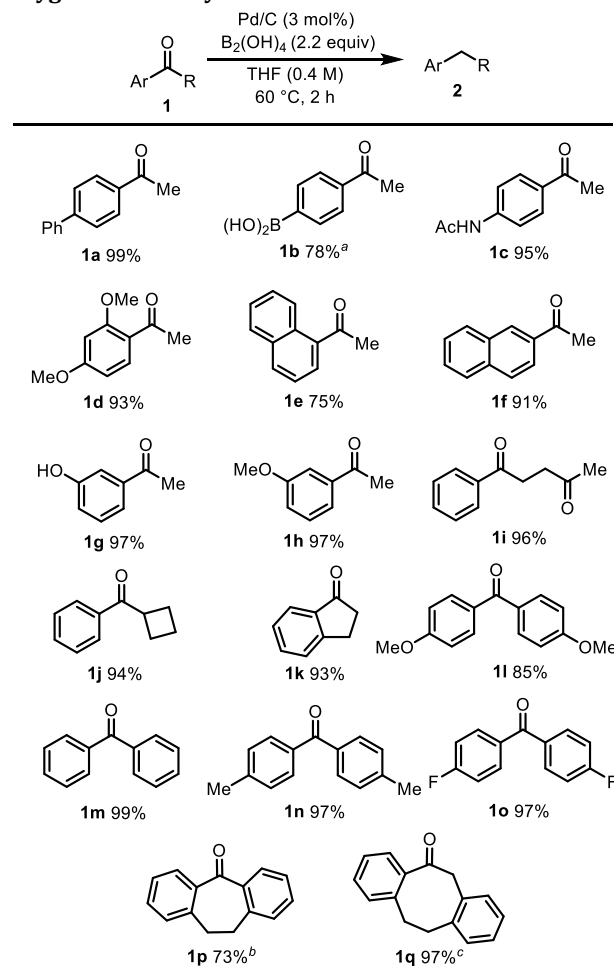
entry	additive(s) (equiv)	yield 2a (%)	D in 2a (%)	yield 3a (%)
1	B ₂ (OH) ₄ (1.1)	20	n/a	54
2	B ₂ (OH) ₄ (2.2)	>95	n/a	0
3 ^a	B ₂ (OH) ₄ (2.2)	78	n/a	18
4 ^b	B ₂ (pin) ₂ (2.2)	trace	n/a	trace
5 ^b	B ₂ (pin) ₂ (2.2) + H ₂ O (5)	70	n/a	20
6 ^c	B ₂ (OD) ₄ (2.2)	>95	85	0
7	B ₂ (OH) ₄ (2.2) + D ₂ O (10)	>95	67	0
8 ^d	B ₂ (OH) ₄ (2.2)	>95	0	0

Reactions were conducted on 0.3 mmol scale in anhydrous THF (<25 ppm H₂O per Karl Fischer titration) under N₂ atmosphere in a sealed one-dram vial unless otherwise noted. Percent conversion, percent yield, and % deuterium incorporation were determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^a Reaction was performed unsealed under a blanket of N₂ on 1.0 mmol scale. ^b Reaction was performed at 80 °C. ^c B₂(OD)₄ was prepared as 85% deuterium enriched. ^d Reaction was performed in *d*-8 THF.

Excitingly, 2.2 equivalents of B₂(OH)₄ load afforded quantitative deoxygenation of **1a** to **2a** (entry 2). A reaction conducted under a blanket of nitrogen in an open system afforded 78% of **2a** and 18% of **3a**, indicating a closed flask is necessary for the success of the reaction. In stark contrast, the use of B₂(pin)₂ instead of B₂(OH)₄ leads to only trace reduction (entry 4), suggesting that the hydrogen atoms are transferred from B₂(OH)₄ and not some other source (such as THF). B₂(pin)₂ proved capable of mediating the deoxygenation if exogenous water is added, though 80 °C is required, and pinacol byproduct complicate the purification (entry 4). Excitingly, 2.2 equivalents of B₂(OD)₄ (85% D) quantitatively deoxygenated **2a** with perfect 85% deuterium incorporation (entry 6); previous methods for deoxygenative deuteration include the use of expensive and typically pyrophoric reagents, such as LiAlD₄ or D₂ gas.^{11,25-28} When 10 equivalents of D₂O with B₂(OH)₄ were employed, quantitative deoxygenation with deuterium incorporation of 67% was observed (entry 7). This result indicates protons from B₂(OH)₄ and deuterons from water exchange and become available for reduction. Lastly, a reaction performed using *d*₈-THF resulted in no deuterium incorporation (entry 8), indicating that THF is not a hydrogen atom donor in the reaction.

Our optimized conditions lend themselves to high yield transfer deoxygenation of a variety of aromatic ketones in addition to *para*-biphenyl-substituted methyl ketone **1a**, which was isolated in 97% yield on 0.5 mmol scale (Table 2). Other methyl phenyl ketones evaluated include *para*-boronic acid (**1b**) and *para*-acetamide (**1c**) derivatives, which were deoxygenated in high yield. *Ortho*-substituted methyl phenyl ketones were also tolerated, as exhibited by

Table 2. Evaluation of the Generality of the Reductive Deoxygenation of Aryl Ketones

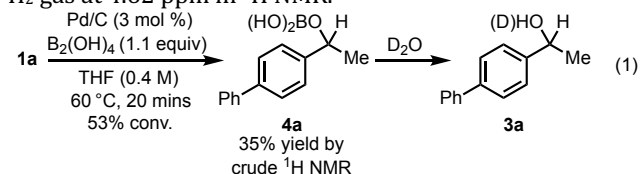


Reactions were conducted on 0.5 mmol scale in anhydrous THF under air in a sealed one-dram vial unless otherwise noted. All yields are isolated unless otherwise noted. ^a Yield was determined using ¹H NMR with 1,3,5-trimethoxybenzene as an internal standard. ^b 3.0 equivalents of B₂(OH)₄ was used. ^c Reaction was performed on 4.70 g (21.2 mmol) scale.

dimethoxyaryl substrate **1d** and 1-naphthyl substrate **1e**, the latter of which reacted more sluggishly. In contrast, 2-naphthyl ketone substrate **1f** afforded **2f** in 91% yield. Two *meta*-substituted methyl phenyl ketones were also cleanly deoxygenated, including free alcohol **1g** (97% yield) and methyl ether **1h** (also 97% yield). Dialkyl ketones proved unreactive in this reaction as shown in the deoxygenation of diketone **1i**, wherein only the aromatic ketone is reduced. Other alkyl aryl ketones that were cleanly reduced include cyclobutyl phenyl ketone **1j** (94%) and 1-indanone **1k** (93%). The retention of the cyclobutane of **1j** suggests that a benzylic radical is not formed during the reaction.²⁹ Four symmetric diaryl ketones were also cleanly deoxygenated, name 4,4'-dimethoxybenzophenone (**1l**), benzophenone (**1m**), 4,4'-dimethylbenzophenone (**1n**), and 4,4'-difluorobenzophenone (**1o**). Conformationally inflexible dibenzosuberone **1p** proved slower to convert and resulted in attenuated yield of 73%. A multigram scale reaction was also performed in high yield using ketone **1q**, and we have been using the dibenzocyclooctadiene product **2q** as a precursor for a model monomer in functional polymer materials synthesis.^{30,31} Lastly it should be noted that a dimethyl aniline

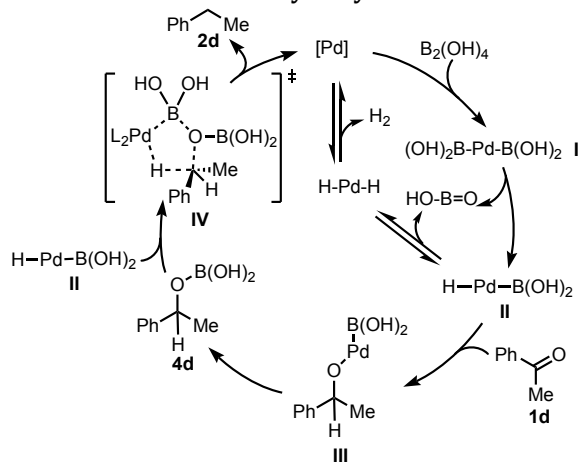
substrate was not converted under the reaction conditions (not shown).

The possibility of a hydroboration event leading to a borate ester was investigated using shortened reaction time and fewer equivalents of $B_2(OH)_4$ to increase the chances of detecting semireduced intermediates (Eq 1). After workup, 1H NMR in $CDCl_3$ revealed a poorly resolved multiplet at 5.50 ppm that, upon addition of D_2O , resolved to a quartet resonance assigned to the benzylic proton of **3a** at 4.94 ppm, indicating hydrolysis (see Figure S5–S7 in the Supporting Information). The benzylic protons of borate esters like **4a** are reported to have characteristic chemical shifts around 5.50 ppm in $CDCl_3$.^{32,33} Isolation of the borate ester was unsuccessful, so further characterization was not possible. Hydrogen evolution has been reported for other transition metal-catalyzed reactions involving $B_2(OH)_4$ although not under anhydrous or additive-free conditions.^{21,22,34,35} To probe H_2 evolution in our system, $B_2(OH)_4$ and Pd/C were stirred in anhydrous THF at 60 °C and the headspace was bubbled into $CDCl_3$ within an NMR tube, which then showed H_2 gas at 4.62 ppm in 1H NMR.³⁶



A putative catalytic cycle is shown in Scheme 2 using acetophenone (**1d**) as a model substrate. Oxidative addition across the B–B bond gives a diboryl complex **I** from which β -hydride elimination could yield H–Pd–B(OH)₂ species **II** and metaborate (HO–B=O), which has been suggested previously.³⁷ Migratory insertion of the carbonyl into the Pd–H bond of **II** could afford alkoxypalladium intermediate **III**, from which reductive elimination could afford borate ester **4d**. Subsequent hydrogenolysis of **4d** by **II** via cyclic transition state **IV** could afford **2d**. An alternative pathway from **1d** to **4d** could involve reaction of **1d** with PdH_2 , as has previously been reported for Pd-catalyzed reduction of aldehydes and ketones to alcohols using HB(pin).³⁸

Scheme 2. Putative Catalytic Cycle



In conclusion, we have developed a new method for the deoxygenation of aromatic ketones in which the sole source of hydrogen atoms is $B_2(OH)_4$. The singly reduced species under anhydrous conditions appears to be a borate ester which is then reduced. High-fidelity deoxygenative deuteration has also been demonstrated using $B_2(OD)_4$.

Additionally, this method should be amenable to the development of selective benzylic perdeuteration of small molecules.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data. This material is available free of charge.

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Notes

The authors declare no competing financial interest.

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