# Metal-free Reduction of Nitro Aromatics to Amines with $B_2(OH)_4/H_2O$

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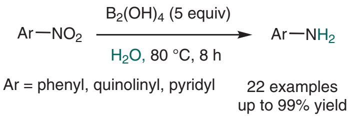

- Metal-free conditions
- Water as both hydrogen donor and solvent
- Good functional group tolerance

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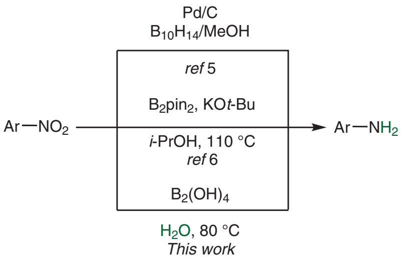
**Abstract** A metal-free reduction of nitro aromatics mediated by diboronic acid with water as both the hydrogen donor and solvent under mild conditions has been developed. A series of aromatic amines were obtained with good functional group tolerance and in good yields.

**Key words** diboronic acid, nitro aromatics, amines, reduction, water

Aromatic amines are important intermediates in the synthesis of numerous nitrogen-containing biologically active compounds, pharmaceuticals, agrochemicals, dyes, and polymers.[1] They are also the precursors for many synthetically useful building blocks, such as amides, imines, diazonium salts, which can be converted into various functional groups.[2] Reduction of nitro aromatics is a most common, short, and facile route to prepare aromatic amines. Since the classic Bechamp reduction was reported for the conversion of nitro aromatics to the corresponding anilines,[3] numerous efforts have been devoted to exploring highly efficient catalysts and reductants, as well as developing simple and green procedures for this transformation.[4] For example, a Pd/C-catalyzed reduction of nitro aromatics with decaborane as the reductant was realized in 2004.[5] Very recently, a reduction of nitro aromatics to the corresponding amines with $B_2pin_2$ in isopropanol has been developed.[6] However, in the above two cases, transition-metal catalyst and organic solvents were required. If water could serve as both the solvent and hydrogen donor under metal-free conditions, the procedure would be greener and more desirable.

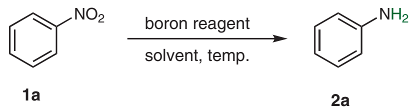
In 2016, the pioneering work about diboronic acid $B_2(OH)_4$-mediated Pd-catalyzed transfer hydrogenation of unsaturated C–C bonds with water as the stoichiometric hydrogen donor was reported by Stokes.[7] After that, the development of transfer hydrogenation with environmentally benign, safe, and cost-efficient water as a hydrogen donor attracted increasing attention. For instance, a Pd-catalyzed transfer hydrogenation of olefins[8] and *N*-heteroaromatics[9] with water as the hydrogen donor assisted by $B_2Pin_2$ has been realized. Furthermore, the $B_2(OH)_4$-mediated hydrogen transfer from water to *N*-heteroaromatics under metal-free conditions has also been achieved.[10] Subsequently, several reductions with water as the hydrogen donor catalyzed by Pd/$B_2pin_2$[11] or Cu/$B_2pin_2$[12] also appeared. Very lately, a Ru-catalyzed reductive amination with $H_2O$ as both the hydrogen source and solvent with a $B_2(OH)_4/H_2O$ system was reported by Song's group.[13] To continue our research interest in the reduction with $B_2(OH)_4$,[11b,14] we herein report a $B_2(OH)_4$-promoted metal-free reduction of nitro aromatics to the corresponding amines with water as both the hydrogen donor and solvent (Scheme 1).



**Scheme 1** Reduction of nitro arenes with boron reagents

The study was initiated by examining the reduction of nitrobenzene (**1a**) with three equivalents of diboronic acid in water. As shown in Table 1, aniline (**2a**) was detected with a GC yield of 59% after 24 h at 40 °C (entry 1). Inspired by Stokes's work,[7] we attempted the reduction in the presence of 0.5 mol% Pd/C; the yield was not improved significantly (entry 2). It was found that the reaction accelerated obviously with increasing temperature. Yields of 57 and 81% of **2a** were detected at 60 and 80 °C, respectively, even shortening the reaction time to eight hours (entries 3–4). To our delight, quantitative yield of **2a** was obtained with five equivalents of diboronic acid (entry 5).[15] No reaction occurred when diboronic acid was replaced by boronic acid [$B(OH)_3$] or pinacolborane [HBpin] (entries 6–7). In addition, diboronic acid esters such as bis(pinacolato)diboron [$B_2pin_2$] and bis(catecholato)diboron [$B_2(cat)_2$] were effective in this reduction, affording **2a** in 31 and 72% yield, respectively (entries 8–9). Next, the reaction was examined in organic solvents including acetonitrile, toluene, methanol, ethanol, and isopropanol. It is worth to note that the reaction in anhydrous aprotic acetonitrile and toluene left the substrate **1a** intact (entries 10–11). The reduction of **1a** did occur in toluene with the addition of 10 equivalents of $H_2O$ (entry 12). The reaction proceeded as well in anhydrous protic solvents, meaning that the alcohols can also act as both the solvent and hydrogen donor (entries 13–15).

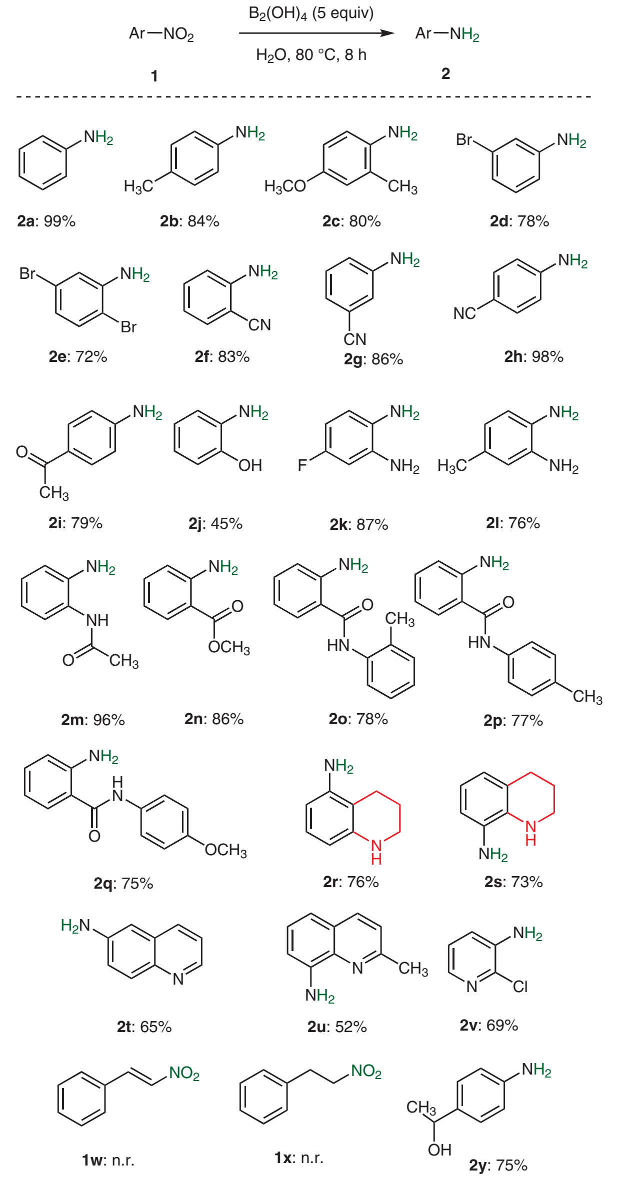
**Table 1** Optimization of Reaction Conditions[a]



| Entry | Boron reagent (equiv) | Solvent | T (°C) | t (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $B_2(OH)_4$ (3) | $H_2O$ | 40 | 24 | 59 |
| 2[c] | $B_2(OH)_4$ (3) | $H_2O$ | 40 | 24 | 61 |
| 3 | $B_2(OH)_4$ (3) | $H_2O$ | 60 | 8 | 57 |
| 4 | $B_2(OH)_4$ (3) | $H_2O$ | 80 | 8 | 81 |
| 5 | $B_2(OH)_4$ (5) | $H_2O$ | 80 | 8 | 99 |
| 6 | $B(OH)_3$ (5) | $H_2O$ | 80 | 8 | 0 |
| 7 | HBpin (5) | $H_2O$ | 80 | 8 | 0 |
| 8 | $B_2pin_2$ (5) | $H_2O$ | 80 | 8 | 31 |
| 9 | $B_2(cat)_2$ (5) | $H_2O$ | 80 | 8 | 72 |
| 10 | $B_2(OH)_4$ (5) | $CH_3CN$ | 40 | 24 | 0 |
| 11 | $B_2(OH)_4$ (5) | toluene | 40 | 24 | 0 |
| 12[d] | $B_2(OH)_4$ (5) | toluene | 40 | 24 | 12 |
| 13 | $B_2(OH)_4$ (5) | MeOH | 80 | 8 | 98 |
| 14 | $B_2(OH)_4$ (5) | EtOH | 80 | 8 | 88 |
| 15 | $B_2(OH)_4$ (5) | *i*-PrOH | 80 | 8 | 23 |

[a] *Reaction conditions*: nitrobenzene (**1a**) (1.0 mmol), solvent (3 mL).
[b] Determined by GC with an internal standard (mesitylene).
[c] 0.5 mol% Pd/C was added.
[d] 10 equiv of $H_2O$ was added.

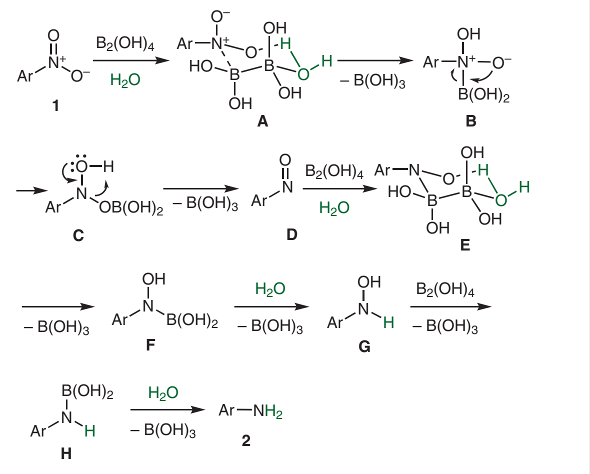
With the optimized reaction conditions in hand, the scope of nitro aromatics was then examined (Scheme 2). The reduction of nitrobenzenes **1b,c** bearing methyl and methoxy groups proceeded smoothly to give the anilines **2b,c** in 84 and 80% yield, respectively. For the labile halogen-substituted nitrobenzenes **1d**, **1e**, and **1k**, the corresponding anilines **2d**, **2e**, and **2k** were obtained in 72–87% yield without dehalogenation. The highly chemoselective reduction of nitrobenzenes **1f–i** containing reducible cyano and carbonyl groups was observed, affording the corresponding anilines **2f–i** in 79–98% yield with the cyano and carbonyl groups remaining intact. The reaction of 2-nitrophenol **1j** with a free phenolic hydroxy group was also investigated, and **2j** was obtained in only 45% yield. Nitrobenzenes **1k–m** with amino and acetyl amino groups were also applicable to this reduction, and the corresponding 1,2-diaminobenzenes **2k–m** were isolated in 76–96% yield. 2-Nitro-



**Scheme 2** Substrate scope. *Reaction conditions*: nitroarene **1** (1.0 mmol), $B_2(OH)_4$ (5.0 mmol), $H_2O$ (3.0 mL), 80 °C, 8 h, isolated yield. n.r.: no reaction

benzoate (**1n**) and 2-nitrobenzamides **1o–q** afforded the reduced products **2n–q** in 75–86% yield. Next, the nitro heteroaromatics such as 5-nitroquinoline (**1r**) and 8-nitroquinoline (**1s**) were investigated. Very interestingly, both the nitro group and pyridine ring were reduced, affording the amino-substituted 1,2,3,4-tetrahydroquinolines **2r** and **2s** in 76 and 73% yield, respectively.[10] However, 6-nitroquinoline (**1t**) and 2-methyl-8-nitroquinoline (**1u**) had relatively lower reactivity, and 6-aminoquinoline (**2t**) and 2-methyl-8-aminoquinoline (**2u**) were isolated in 65 and 52% yield, respectively, and the pyridine ring remained intact. In addition, the nitro pyridine **1v** was also applicable to this reduction. The nitro group of **1v** was reduced with the pyridine ring remaining intact, giving the product **2v** in 69% yield. Next, the α,β-unsaturated nitro compound **1w** and aliphatic nitro compound **1x** were also examined, but no reaction occurred. Finally, enantiopure (*S*)-1-(4-nitrophenyl)ethan-1-ol (**1y**) with 83% ee was also reduced under the optimized reaction conditions, but a racemic compound **2y** was obtained in 75% yield.

Inspired by the reaction mechanism in the reduction of aromatic nitro compounds to aromatic amines with $B_2pin_2$ in isopropanol,[6] a plausible reaction pathway was proposed (Scheme 3). Initially, the nitro aromatic **1** coordinates with $B_2(OH)_4$ and $H_2O$ to form a six-membered ring transition state **A**, which eliminates $B(OH)_3$ to afford intermediate **B**. Then nitroso aromatic **D** is formed by rearrangement of **B** and cleavage of the N–O–$B(OH)_2$ bonds of **C**. Once again, the nitroso aromatic **D** coordinates with $B_2(OH)_4$ and $H_2O$ to form a six-membered ring transition state **E**, which releases $B(OH)_3$ to afford intermediate **F**.



**Scheme 3** A possible reaction pathway

The hydroxylamine **G** is generated after hydrolysis of **F**. Then, **G** reacts with $B_2(OH)_4$ to give intermediate **H** by releasing $B(OH)_3$. The desired aromatic amine **2** is obtained through hydrolysis of **H**.

In summary, we have developed a facile reduction of nitro aromatics mediated by $B_2(OH)_4$ in water under metal-free conditions. A possible reaction pathway was also proposed. Further investigations devoted to the mechanism and synthetic application of this method are ongoing in our laboratory.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610086.

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(15) **Aniline (2a)**
Nitrobenzene (123 mg, 1.0 mmol), $B_2(OH)_4$ (448 mg, 5.0 mmol, 5.0 equiv), and $H_2O$ (3.0 mL) were added to a 10 mL tube. The reaction mixture was stirred at 80 °C for 8 h. When the reaction was complete (monitored by TLC), the mixture was cooled to r.t. and extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried with anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. Colorless oil (92 mg, 99%); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.27–7.22 (m, 2 H), 6.87–6.83 (m, 1 H), 6.76 (dd, $J_1$ = 7.6 Hz, $J_2$ = 0.8 Hz, 2 H), 3.66 (br, 2 H) ppm; $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ = 146.60, 129.49, 118.72, 115.30 ppm.