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Metal-Free Reduction of Aromatic Nitro Compounds to Aromatic Amines with B_2pin_2 in Isopropanol

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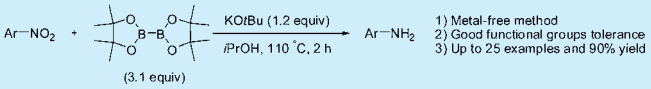
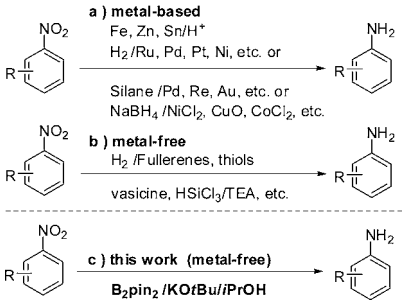
Supporting Information

ABSTRACT: A metal-free reduction of aromatic nitro compounds to the corresponding amines has been achieved by a combination of B_2pin_2 and KO*t*Bu in isopropanol. A series of nitro compounds containing various reducible functional groups were chemoselectively reduced in good to excellent yields.



Reduction of functionalized aromatic nitro compounds to aromatic amines is a valuable reaction due to the fact that the products are widely used as central intermediates and key precursors in the synthesis of many pharmaceuticals, dyes, agrochemicals, and polymers.[1] Plentiful strategies have been developed to complete this transformation. In general, this transformation has been accomplished mainly by two methods. (1) Metal-based methods: the reactions using a large excess of Zn, Fe, or $SnCl_2$ in the presence of an acid are usually considered to be the classical reduction methods.[2] The metal catalytic hydrogenation in the presence of H_2 or stoichiometric amounts of other reducing agents can also reduce nitro groups (Scheme 1a).[3] Recently, Beller and co-workers developed some excellent

Scheme 1. Different Methods for the Reduction of Aromatic Nitro Compounds



Co_3O_4 and Fe_2O_3 based heterogeneous catalysts for the hydrogenation of nitroarenes.[4] (2) Metal-free methods: these available methods incorporate the use of 9,10-dihydroanthracene,[5] 1,4-dihydropyridines,[6] thiols,[7] (2-pyridyl)phenylmethanol,[8] fullerenes/H_2,[9] reduced grapheme oxide/hydrazine-hydrate,[10] and vasicine.[11] Moreover, Benaglia et al. reported the chemoselective reduction of aromatic and aliphatic nitro compounds to amines by using $HSiCl_3$ with TEA[12] (Scheme 1b). Although several of these protocols have been used widely, there are still some drawbacks: the lack of chemoselectivity, the use of special high pressure equipment, inflammable hydrogen gas, hazardous reagents, relatively expensive metal complexes, and long reaction times. Given these facts, it is still very desirable to develop new, economical, and efficient methods for the highly chemoselective reduction of aromatic nitro compounds, especially under mild and user-friendly conditions.

Bis(pinacolato)diboron (B_2pin_2) is widely used as a stable, green, and cheap reagent in borylation reactions.[13] The combination of B_2pin_2 and a Lewis base, in particular, has been recognized as an efficient reagent for the metal-free borylation of some special molecules.[14] However, the direct use of these reagents for reduction has been rarely studied. Recently, Mahesh K. Lakshman and Jacques Einhorn et al. disclosed the facile reduction of amine *N*-oxides and cleavage reaction of the N—O—H bonds based on the use of B_2pin_2, independently.[15] To the best of our knowledge, no synthetic route to aromatic amines by reduction of aromatic nitro compounds with B_2pin_2 has been reported. Herein, we report a novel protocol for the chemoselective reduction of aromatic nitro compounds to the corresponding amines using B_2pin_2 activated by KO*t*Bu in isopropanol (Scheme 1c).

Our initial studies were carried out by examining 1-bromo-4-nitrobenzene (**1a**, 1.0 equiv) and B_2pin_2 (**2**, 3.0 equiv) in the presence of Cs_2CO_3 in MeOH at 80 °C for 8 h (Table 1, entry 1). The desired product **3a** was observed in 85% yield in LC-MS without byproducts. Encouraged by this preliminary result, various bases were studied, and an excellent yield of **3a** was afforded when KO*t*Bu was employed (entry 5). In addition, almost no reaction occurred in the presence of other weaker bases (entries 2, 3) or some organic bases (see Supporting Information). Notably, the reaction did not work without a base (entry 8), so the base is essential for this reaction.

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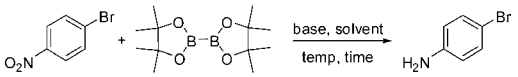
Table 1. Optimization of the Reaction Conditions[a]



1a 2 3a

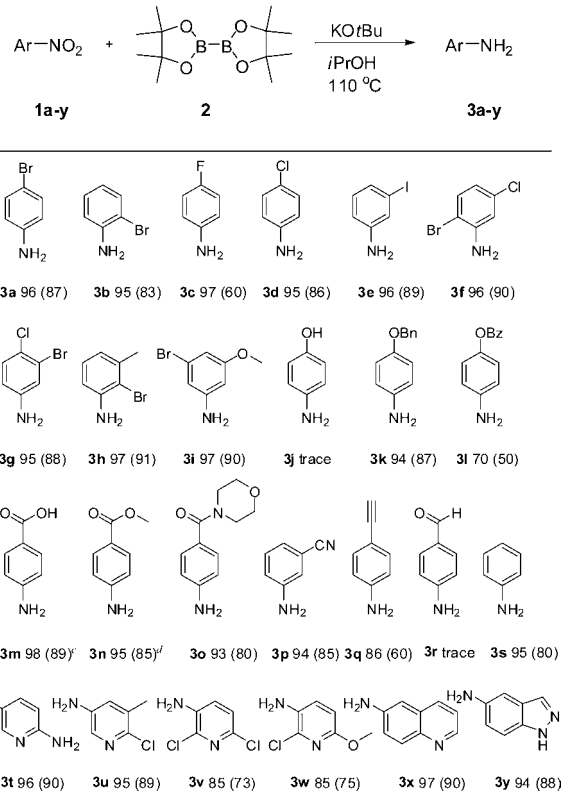
entry	base (equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1	Cs_2CO_3 (2.0)	MeOH	80	8	85
2	Na_2CO_3 (2.0)	MeOH	80	8	trace
3	K_2CO_3 (2.0)	MeOH	80	8	trace
4	NaOMe (2.0)	MeOH	80	8	80
5	KO*t*Bu (2.0)	MeOH	80	8	89
6	NaO*t*Bu (2.0)	MeOH	80	8	75
7	LiO*t*Bu (2.0)	MeOH	80	8	74
8	–	MeOH	80	8	n.r.
9	KO*t*Bu (2.0)	EtOH	80	8	89
10	KO*t*Bu (2.0)	*i*PrOH	80	8	91
11	KO*t*Bu (2.0)	*t*BuOH	80	8	84
12	KO*t*Bu (2.0)	dioxane	80	8	12
13	KO*t*Bu (2.0)	THF	80	8	9
14	KO*t*Bu (2.0)	toluene	80	8	13
15	KO*t*Bu (2.0)	H_2O	80	8	trace
16[c]	KO*t*Bu (1.2)	*i*PrOH	80	8	88
17[c]	KO*t*Bu (0.5)	*i*PrOH	80	12	70
18[c]	KO*t*Bu (1.2)	*i*PrOH	50	24	65
19[c]	KO*t*Bu (1.2)	*i*PrOH	rt	24	trace
20[c]	KO*t*Bu (1.2)	*i*PrOH	110	2	96/87[d]

[a]Reaction conditions: **1a** (1.0 mmol), **2** (3.0 mmol), base (2.0 mmol), 4.0 mL of solvent, 80 °C. [b]HPLC yield. [c]3.1 equiv of **2**. [d]Isolated yield. n.r. = no reaction.

Through the screening of solvents, protic solvents were found to achieve higher yields in the reaction except for H_2O (entry 15). By contrast aprotic solvents were less effective (entries 9−11 vs 12−14). *i*PrOH was found to be the best solvent (91%, entry 10).[16] Furthermore, we found that the yield of the product was not affected when the amount of KO*t*Bu decreased to 1.2 equiv (88% yield, entry 16). When the amount of KO*t*Bu was decreased to the catalyst loading amount (entry 17), the starting material **1a** was not completely consumed. By increasing the amount of B_2pin_2 to 3.1 equiv the conversion of the starting material increased (see Supporting Information). The reaction temperature was also screened. Lowering the reaction temperature did not favor the reaction, even when prolonging the reaction time to 24 h (entries 18, 19). High temperature can promote this transformation, and 96% of desired product was achieved at 110 °C in 2 h (entry 20). Additionally, some other boron sources were investigated (see Supporting Information) and the results indicated that diboron reagents are the most suitable ones to accomplish this reaction in good yields. Finally, the optimized reaction conditions for the reduction of aromatic nitro compounds (1.0 equiv) to the corresponding aromatic amines were determined as the combination of B_2pin_2 (3.1 equiv) with KO*t*Bu (1.2 equiv) in *i*PrOH at 110 °C for 2 h.

With the optimal reaction conditions in hand, the scope of the reduction of aromatic nitro compounds was explored (Scheme 2). The nitro group is chemoselectively reduced in the presence of all halogen groups in our protocol, which afford the desired halogenated anilines in good to excellent yields (60%−91%), and without any dehalogenation in these cases (**3a**−**3i**). The reactivity of 4-nitrophenol was not effective, even when increasing the equivalents of KO*t*Bu and extending the reaction time, which could be attributed to the acidity of the phenolic

Scheme 2. Reduction of Various Nitro Compounds with B_2pin_2[a,b]



[a]Standard reaction conditions: **1** (1.0 mmol), **2** (3.1 mmol), KO*t*Bu (1.2 mmol) in 4 mL of *i*PrOH at 110 °C for 2 h (as to the heterocyclic nitro compounds, the reaction time is 0.5 h). [b]Determined by LC-MS analysis of the crude reaction mixture, with the isolated yield in parentheses. [c]Isolated as 4-acetylamino benzoic acid. [d]Isolated as a mixture of **3n** and isopropyl 4-aminobenzoate.

hydroxyl group (**3j**). 4-Nitrophenol containing protecting groups such as benzyl and benzoyl can be reduced in moderate to good yields (**3k** and **3l**). 4-Nitrobenzoic acid was reduced in high yield (89%) by increasing the amount of KO*t*Bu to 2.5 equiv. The excess base was used for neutralizing the acidity of the substrate initially, and the product was isolated as 4-acetylamino benzoic acid for easy purification (**3m**). Ester groups also tolerated the reaction conditions, and a mixture of **3n** and isopropyl 4-aminobenzoate was obtained, because of the transesterification of methyl 4-nitrobenzoate. Nitrobenzene with an amide functional group was also smoothly reduced in high yield (**3o**). It is noteworthy that some reducible functional groups such as cyano and alkynyl are minimally affected under our conditions (**3p**, **3q**). However, because of the reduction of the aldehyde group, 4-nitrobenzaldehyde gives the desired aniline in trace yield with a complex mixture even in low temperature under these conditions (**3r**). Nitrobenzene can be reduced by extending the time, and a moderate yield was observed (**3s**). This transformation can also be successfully extended to heterocyclic nitro compounds to form the corresponding heterocyclic aromatic amines in 73−90% yields within 30 min (**3t**−**3y**).

To gain insight into the reaction mechanism, a series of control experiments and ^{11}B NMR experiments were performed (see Supporting Information). When B_2pin_2 or KO*t*Bu was used alone, there is no reaction under optimal conditions. A major

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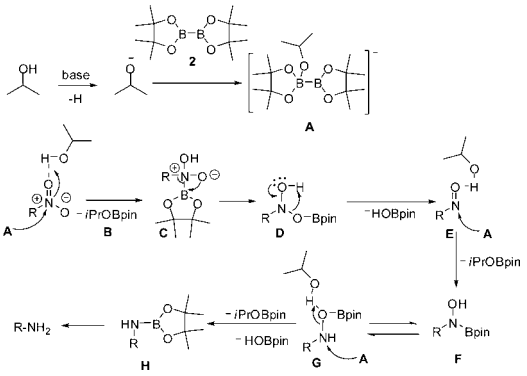
peak at 22.3 ppm was observed in the ^{11}B NMR spectrum of the reaction mixture, which was consistent with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*i*PrOBpin), and this byproduct was also detected by GC-MS. More than 3.0 equiv of B_2pin_2 are needed in this reaction. Based on the results mentioned above and the literature reports, a putative reaction pathway is shown in Scheme 3.[12] Initially, isopropanol is

Scheme 3. Possible Mechanism



deprotonated by KO*t*Bu to form an isoproxide anion, which then reacts with B_2pin_2 (**2**) to generate anionic sp^2-sp^3 diborane reagents (**A**) $[B_2pin_2iPrO]^-$.[14] The nucleophile (**A**) attaches the electrophilic nitrogen atom to remove *i*PrOBpin (**B**) and produce an intermediate (**C**). Then nitroso benzene (**E**) is formed by rearrangement of **C** and cleavage of the N−O−Bpin bonds of **D**. Further, nitroso benzene (**E**) reacts with **A** to obtain **G** which is an analogue of hydroxylamine (**F**). **G** reacts with **A** through nucleophilic reactions to provide **H**. Finally, intermediate **H** was protonated to give the desired product. Although the mechanism involving sp^2-sp^3 diborane reagents is reported here for simplicity, the deoxygenation may be a complex process, with more than one contributing pathway.[17]

In summary, we have developed a novel and highly efficient method for the reduction of aromatic nitro groups to amines using commercially available B_2pin_2 reagents. This reaction does not require any metal, high pressure equipment, or flammable hydrogen gas. In addition, other notable features are its short reaction times, generally high yields, and broad functional group tolerance. Further investigations devoted to the mechanism and synthetic applications of this method are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01274.

Experimental details, characterizations, and NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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