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Graphical Abstract

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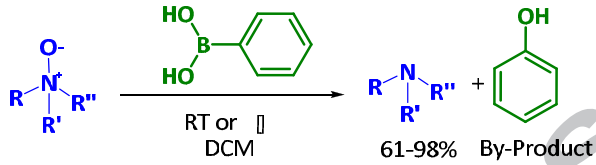

R, R' & R'' = Aryl, alkyl and hetero aromatic

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ABSTRACT

A simple and efficient method for the deoxygenation of amine *N*-oxides to corresponding amines is reported using the green and economical reagent phenylboronic acid. Deoxygenation of *N*, *N*-dialkylaniline *N*-oxides, trialkylamine *N*-oxides and pyridine *N*-oxides were achieved in good to excellent yields. The reduction susceptible functional groups such as ketone, amide, ester and nitro groups are well tolerated with phenylboronic acid during the deoxygenation process even at high temperature. In addition, an indirect method for identification and quantification of *tert*-amine *N*-oxide is demonstrated using UV-Vis spectrometry which may be useful for drug metabolism studies.

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Amine *N*-oxides have found wide application in synthetic organic chemistry as starting materials, intermediates, oxidants, ligands, organo catalysts, directing groups, etc.[1] Besides their chemical importance, *N*-oxides have also received considerable attention in the field of biology and medicine.[2] Many findings suggest that *N*-oxides play a key role in the metabolism of drugs.[2b] Moreover, the chemistry of deoxygenation of amine *N*-oxides has attracted significant interest not only in synthetic organic chemistry[3] but also in biology.[4] Recently, fluorescent probes have been developed based on deoxygenation of *N*-oxides for sensing metal and non-metal species found in biological assays (Figure 1).[4a-c] In medicine, *N*-oxides have been suggested as less toxic bio-reductive prodrugs for anticancer drugs (i.e. DNA intercalators) that are selectively deoxygenated to the active drug by metabolic reduction under hypoxic conditions (Figure 2). [4d, 4e]

Considering the importance of deoxygenation processes in chemical and biological transformations, numerous deoxygenation methods have been developed using various metal and metal free reagents including Pd-C/$HCOONH_4$,[5] Zn/NH_4Cl,[6] CuI,[7] $ZrCl_4$/$NaBH_4$,[8] SmI_2,[9] In/NH_4Cl,[10] titanium compounds,[11] sulfur reagents,[12] phosphorus reagents,[13] diboron compounds[14], etc. The major limitations of these existing protocols are the use of toxic metals or expensive reagents or reagents that are difficult to handle (e.g. unpleasant odor, fuming, flammable or hygroscopic), requirement of harsh and dry reaction conditions, longer reaction times, functional group incompatibilities, etc.

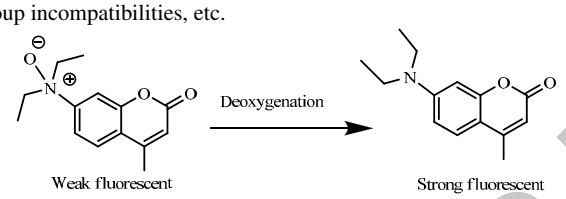
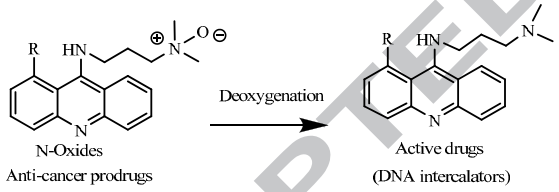


Figure 1. Example of *N*-oxide deoxygenation promoted turn-on fluorescent probe.



R = H; **DAPA:** 9-[3-(N,N-dimethylamino)propylamino]acridine;
R = NO_2; **NC:** nitracrine;
R = NH_2; **AC:** 1-amino-9-[3-(N,N-dimethylamino)propylamino]acridine

Figure 2. Structures of *N*-oxide based anticancer prodrugs.

Therefore, the development of an efficient and convenient method for the selective reduction of amine *N*-oxides using green reagents will have high significance not only in synthetic organic chemistry but also in biological science, for example, drug metabolism studies.[11c]

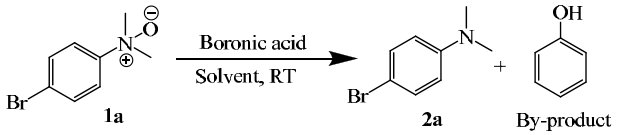
Organoboron compounds are important reagents in synthetic organic chemistry which enable many chemical transformations in an efficient manner.[15] Among the different subclasses of organoboron compounds, arylboronic acids remain the most popular and extensively used in organic synthesis as building blocks, intermediates, reagents and catalysts.[15a] Properties such as low toxicity, high stability (against air, moisture and temperature) and good chemical reactivity as well as ease of handling and storing make arylboronic acids a more attractive class of compounds in organic synthesis. Our research group is mainly interested in developing eco-friendly methods for the preparation of important organic compounds.[16] In fact, we have recently reported efficient and green methods for the oxidation of arylboronic acids into phenols using hydrogen peroxide derivatives.[16b, 16c] In this context, here we report phenylboronic acid as an efficient reagent for the deoxygenation of *tert*-amine *N*-oxides under mild conditions.

At the outset, 4-bromo-*N*,*N*-dimethylaniline *N*-oxide (**1a**) was chosen as a model substrate for reaction optimization while phenylboronic acid was used as a deoxygenating reagent (Table 1). In order to identify a suitable solvent, the deoxygenation reactions were carried out in different protic and aprotic solvents at room temperature using equimolar amount of substrate and the reagent (Table 1, entries 1-11). The protic solvents such as methanol, ethanol, *t*-butanol and water gave incomplete reactions even after prolonged reaction time (Table 1, entries 1-5). In the case of polar aprotic solvents (Table 1, entries 6-11), dichloromethane was found to be very efficient, providing a quantitative yield of the desired *tert*-amine within 5 minutes (Table 1, entry 10). In addition, tetrahydrofuran, 2-methyl tetrahydrofuran (2-MeTHF) as well as dichloroethane also showed comparable efficiency to that of dichloromethane (Table 1, entries 6, 7 and 11) while toluene and acetonitrile were found to be inefficient media (Table 1, entries 8 and 9).

After identifying dichloromethane as a suitable solvent, the optimization was further continued by examining the deoxygenation process with electron rich and electron deficient arylboronic acids as well as alkylboronic acids as reducing agent (Table 1, entries 12-15). 4-Methoxyphenylboronic acid showed equal efficiency to that of simple phenylboronic acid while 4-nitrophenylboronic acid took slightly longer time for completion of the reaction (Table 1, entries 12 and 13). On the other hand, alkylboronic acids such as methyl and *n*-butylboronic acid showed less efficiency than arylboronic acids in the deoxygenation process, perhaps due to migratory aptitude of alkyl groups[17] (Table 1, entries 14 and 15). Overall, phenylboronic acid was found to be superior among the different boronic acids used in this study in terms of not only higher reactivity but also availability and cost effectiveness. Moreover, phenylboronic acid produces environmentally benign by-products such as boric acid and phenol during the deoxygenation process which can be easily removed by simple basic workup procedures.

It is important to mention here that recently diboron compounds such as bis(pinacolato)diboron [$(pinB)_2$], bis(catecholato)diboron [$(catB)_2$] and tetrahydroxydiboron have been explored as deoxygenating reagents for the amine *N*-oxides.[14] Despite the efficiency of diboron compounds, their high cost and limited availability reduce their use in organic synthesis.[15a, 18] Moreover, in the case of diboron reagents two boron atoms are required to deoxygenate one oxygen atom, while only one boron atom is utilized in the case of phenylboronic acid. Nevertheless, being an economical reagent, phenylboronic acid showed a comparable efficiency to that of diboron compounds in the deoxygenation process. For example, the deoxygenation of *N*-oxide **1a** was achieved in a quantitative yield within 5 minutes using diboron compounds (Table 1, entries 16-18) as well as phenylboronic acid (Table 1, entry 10) in dichloromethane at room temperature.

Table 1: Optimization of reaction conditions.[a]



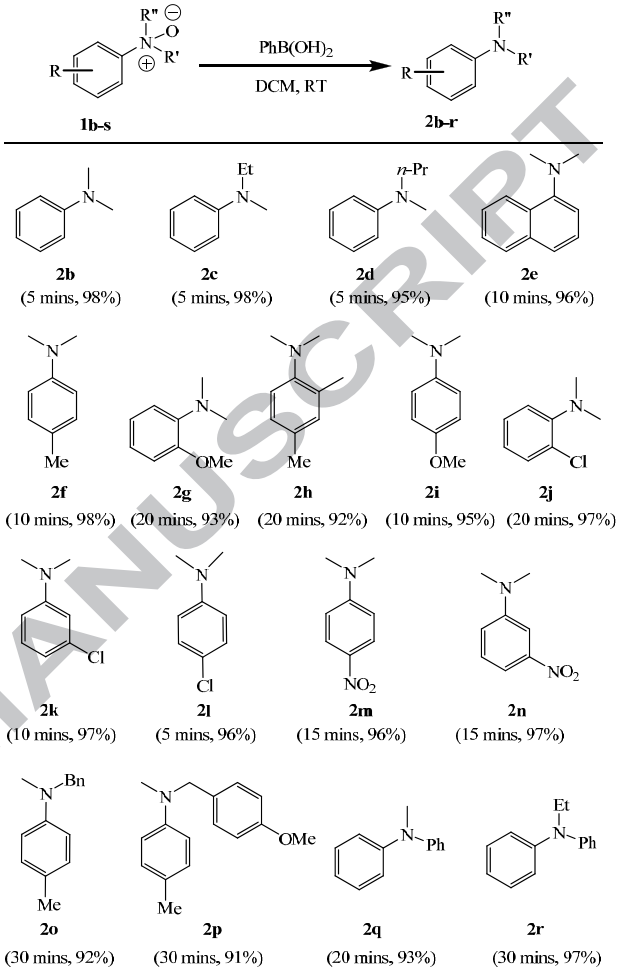
Entry	Solvent	Boronic Acid	Time (mins)	Yield (2a) (%)[b]
1	CH_3OH	$PhB(OH)_2$	60	25
2	CH_3OH	$PhB(OH)_2$	12 h	80
3	C_2H_5OH	$PhB(OH)_2$	60	32
4	*t*-BuOH	$PhB(OH)_2$	60	50
5	H_2O	$PhB(OH)_2$	60	30
6	THF	$PhB(OH)_2$	30	89
7	2- Me THF	$PhB(OH)_2$	15	95
8	Toluene	$PhB(OH)_2$	60	46
9	CH_3CN	$PhB(OH)_2$	60	32
10	DCM	$PhB(OH)_2$	5	97
11	DCE	$PhB(OH)_2$	10	97
12	DCM	*p*-Me-$PhB(OH)_2$	5	97
13	DCM	*p*-NO_2-$PhB(OH)_2$	120	94
14	DCM	$MeB(OH)_2$	60	40
15	DCM	n-$BuB(OH)_2$	60	43
16	DCM	$(pinB)_2$	5	97
17	DCM	$(catB)_2$	5	97
18	DCM	$B_2(OH)_4$	5	97

[a]Reaction condition: aniline *N*-oxide (1 mmol) and boronic acid (1 mmol) stirred in different solvents at room temperature. [b]Isolated yield. [c]$(pinB)_2$: bis(pinacolato)diboron. [d]$(catB)_2$: bis(catecholato)diboron.

With optimized conditions in hand, the deoxygenation of various aniline *N*-oxides was studied with phenylboronic acid at room temperature (Table 2). Un-substituted *N*,*N*-dialkylaniline *N*-oxides as well as naphthylamine *N*-oxides have been successfully reduced to corresponding amines in excellent yields within 10 mins (Table 2, entries **2b**-**2e**). Similarly, electron donating (e.g. methoxy and methyl) and withdrawing groups (e.g. chlorine, bromine and nitro) functionalized aniline *N*-oxides underwent deoxygenation smoothly to provide the desired products in high yield (i.e. > 90%) at room temperature (Table 2, entries **2f**-**2n**). In fact, no significant electronic effects were observed in the deoxygenation process with respect to different substituents present on the aryl ring. Moreover, sterically hindered (i.e. *ortho* substituted) dialkylaniline *N*-oxides as well as *N*-benzyl and *N*-phenyl aniline *N*-oxides also underwent deoxygenation with same efficiency like simple aniline *N*-oxides (Table 2, entries **2g**, **2h, 2j** and **2o**-**2r**).

Having successful results in hand, we have further examined the reduction of trialkylic (cyclic and acyclic) and benzylic *N*-oxides under optimized condition (Table 3). Initially, the deoxygenation of *N*-methylmorpholine *N*-oxide was performed with one equivalent of phenylboronic acid at room temperature. However, the reaction was found to be slow and the desired product was obtained only in 65% yield after 12 h (Table 3, entry **4a**). Thus, the reaction was performed at 80 °C in 1,2-dichloroethane (DCE) using one equivalent of phenylboronic acid. It is interesting to note that the deoxygenation of *N*-methylmorpholine *N*-oxide proceeded efficiently and gave the desired product (i.e. *N*-methylmorpholine) in 93% yield within 30 minutes (Table 3, entry **4a**). In addition, various cyclic, acyclic and benzylic *N*-oxides were also successfully converted to corresponding amines in excellent yields (Table 3, entries **4b-4g**).

Table 2: Deoxygenation of *N*,*N*-dialkylaniline *N*-oxides using phenylboronic acid.[a,b]

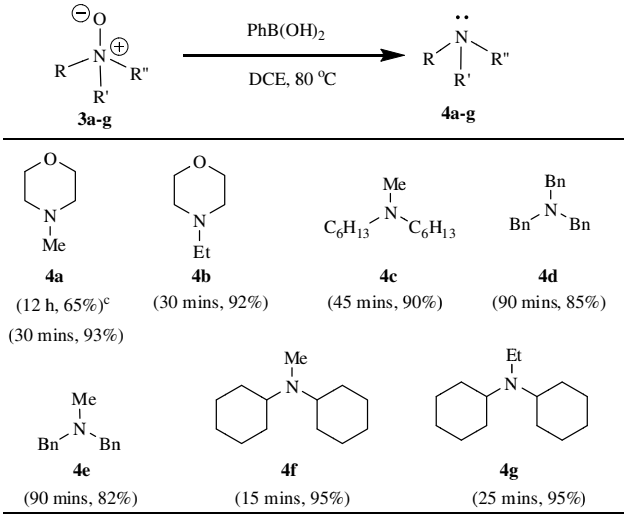


[a]Reaction condition: aniline *N*-oxide (1 mmol) and phenylboronic acid (1 mmol) was stirred in dichloromethane at room temperature. [b]Isolated yield.

The deoxygenation of heteroaromatic *N*-oxides (e.g. pyridine *N*-oxide) has found wide scope in synthetic organic chemistry.[3] Being successful in the case of deoxygenation of aniline and alkyl *N*-oxides, we have attempted the deoxygenation of pyridine and quinoline *N*-oxides with phenylboronic acid (Table 4). The reaction provided the desired products in good to excellent yields with 1.5 equivalents of phenylboronic acid, however at high temperature (i.e. 120 °C). Pyridine *N*-oxides with electron donating groups such as 2,6-dimethyl and 4-(*N*,*N*-dimethylamino)pyridine *N*-oxides underwent smooth conversion with good yield (75-90%) in a short span of time (Table 4, entries **6a** and **6b**). On the other hand, electron deficient pyridine *N*-oxides such as 2-chloro, 4-acetyl, 3-amido and 2,6-dimethyl esters functionalized pyridine-*N*-oxides took slightly longer reaction time and gave the desired products in moderate yields (Table 4, entries **6c**-**6f**). In addition, similar to pyridine *N*-oxides, quinoline and *iso*-quinoline *N*-oxides underwent deoxygenation in 80% and 70% yields, respectively (Table 4, entries **6g** and **6h**). The stability of different functional groups under standard reaction conditions plays a major role in organic synthesis. It is noteworthy that many reduction susceptible functional groups such as ketone, amide, esters and nitro groups are well tolerated with phenylboronic acid during the deoxygenation even at high

temperature (Table 2 and 4). Thus, phenylboronic acid can be regarded as a chemo-selective reducing agent.

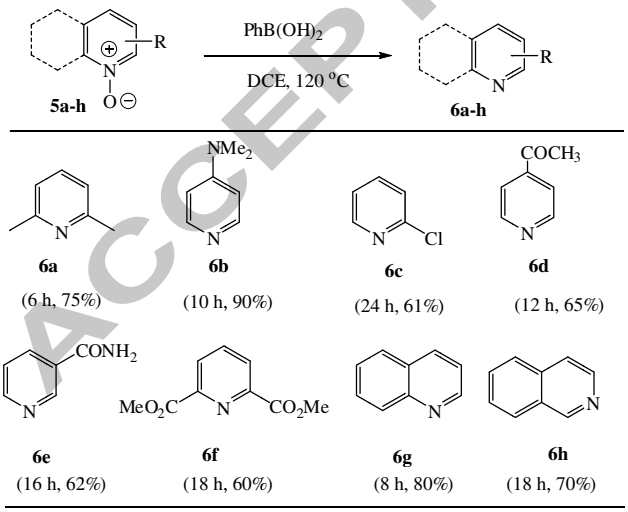
Table 3: Deoxygenation of trialkyl and benzylamine *N*-oxides with phenylboronic acid.[a,b]



[a]Reaction condition: trialkyl *N*-oxide (1 mmol) and phenylboronic acid (1 mmol) was stirred in dichloroethane at 80 °C. [b]Isolated yield. [c]Reaction was carried out at room temperature.

Amine functionalities were found in many drug molecules and play an important role in exerting their biological activity.[19] It is well known that in Phase I metabolism, drugs undergo different chemical modifications like oxidation, reduction or hydrolysis to make more water soluble compounds that can be excreted by various processes.[20] In this context, *N*-oxides have been observed as one of the major metabolites of *tert*-amine drugs.[2b] For example, clozapine *N*-oxide is a major metabolite of anti-depressant drug clozapine.[21] The identification and quantification of *N*-oxide metabolites can play an important role in developing newer drugs with high potential and low toxicity.[20]

Table 4: Deoxygenation of heteroaromatic *N*-oxides with phenylboronic acid.[a,b]

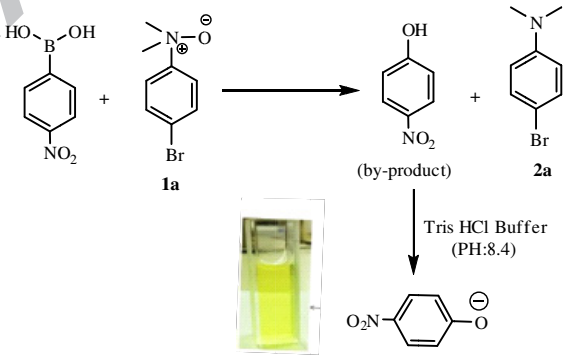


[a]Reaction condition: *N*-oxide (1 mmol) and phenylboronic acid (1.5 mmol) was stirred in dichloroethane at 120 °C. [b]Isolated yield.

Recently, Kulanthaivel *et al.* have demonstrated a chemical deoxygenation method suitable for drug metabolism studies.[11c] Titanium trichloride ($TiCl_3$) has been employed as a selective deoxygenating reagent of amine *N*-oxide metabolites while the reaction progress and analysis were performed using liquid

will be interesting to find an inexpensive method that requires simple instrumentation for a quick identification and quantification of amine *N*-oxides. In this context, we anticipated that a simple indirect method for the detection of *tert*-amine *N*-oxides is possible in UV-Vis spectrometry by using 4-nitrophenylboronic acid as a deoxygenating reagent. Because, 4-nitrophenylboronic acid will produce 4-nitrophenol as a by-product during the deoxygenation of *N*-oxides and it is detectable even at a trace amount at 400 nm in UV-Vis spectrometer.[22,23] Based on the concentration of 4-nitrophenol, *tert*-amine concentration can be easily calculated using Beer-Lambert's law which will provide a significant information regarding the concentration of *N*-oxide. Moreover, other metabolites like sulfoxides and *C*-hydroxylation products can be easily distinguished from *N*-oxides since they are un-reactive with arylboronic acids.

As a case study, the deoxygenation of aniline *N*-oxide **1a** with 4-nitrophenylboronic acid was carried out in acetonitrile at room temperature (Scheme 1).[24] The progress of the reaction was monitored by using UV-Vis spectrometry in every 15 minutes and observed spectra are summarized in Figure 3. The spectrum clearly shows an increase in absorption intensity at 400 nm in Tris-HCl buffer solution, which corresponds to the formation of 4-nitrophenol (Figure 3). The rate of the reaction was calculated from absorbance *vs* time plot and found to be 1.41×10^{-4} s^{-1} (See supporting information Figure **S1 b**). The amount of p-nitrophenol (*p*-NP) formation can be directly correlated with the amount of formation of *tert*-amine from corresponding *N*-oxide.



Scheme 1. Deoxygenation of *N*-oxide **1a** with 4-nitrophenylboronic acid.

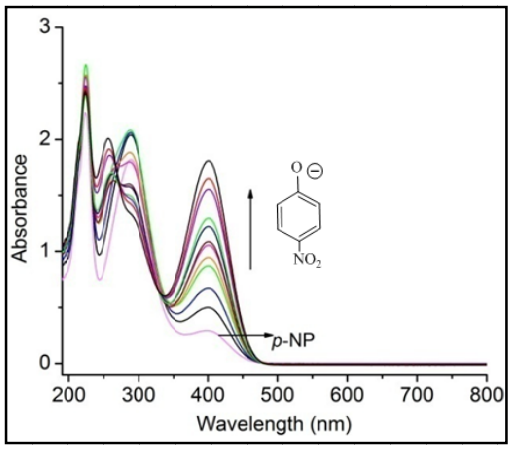


Figure 3. Spectral profile showing the increase of *p*-NP band at 400 nm with respect to time. The reaction was carried out in acetonitrile and spectra were measured in tris-HCl buffer solution with 15 min interval.

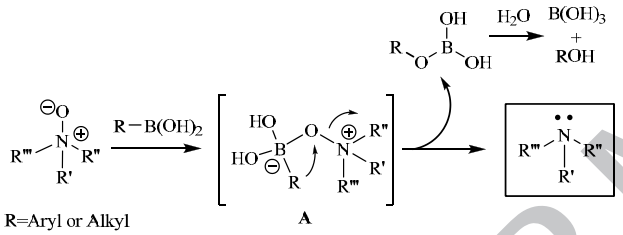
UV experiment. For example, after 60 minutes the isolated yield was about 34% while the calculated UV yield was 39% (Table 5, entry 1). Similarly, the yields obtained in various intervals, for example, after two hours and three hours (in both isolated as well as UV-Vis experiment) were found to be similar (Table 5, entries 2 and 3), which confirms our preliminary assumption.

Table 5. Yield comparison between isolated and calculated from UV for the deoxygenation reaction of **1a** with 4-nitrophenylboronic acid.

Entry	Time	UV yield (%)[a]	Isolated yield (%)[b]
1	1 h	39	34
2	2 h	54	46
3	3 h	81	70

[a]Yield was calculated using Beer-Lambert's law (A= cl) (Refer supporting information). [b]Yield from batch reaction in 1.0 mmol scale.

A plausible mechanism for the deoxygenation of amine *N*-oxide is shown in Scheme 2. At first, *N*-oxide attacks the electrophilic aryl/alkylboronic acid and forms an unstable amino-borate complex **A**.[15a] Further, the aryl/alkyl group migrates from boron to *N*-oxide oxygen which results in formation of *tert*-amine and borate ester. The unstable borate ester further undergoes degradation to boric acid and alcohol in the presence of water.



Scheme 2. Plausible mechanism for the deoxygenation of amine *N*-oxides to corresponding amines.

In conclusion, we have demonstrated a simple and efficient method for the deoxygenation of amine *N*-oxides to corresponding amines using the green and economical reagent phenylboronic acid. The *N*,*N*-dialkylaniline *N*-oxides, trialkylamine *N*-oxides and pyridine *N*-oxides underwent deoxygenation smoothly to provide the desired amines in good to excellent yields. The reduction susceptible functional groups such as ketone, amide, ester, nitro and arylhalides are well tolerated with phenylboronic acid during the deoxygenation process even at high temperature. An indirect method for identification and quantification of *tert*-amine *N*-oxide in UV-Vis spectrometry is demonstrated by using 4-nitrophenylboronic acid as a deoxygenating reagent. We believe that this technique will be useful for drug metabolism studies.

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17. As per mechanism (see Scheme 3), migration of aryl or alkyl group is necessary to obtain the desired amine. In general migration efficiency of alkyl groups are relatively less when compare to aryl groups. We belive it may be a reason for less reactivity of alkylboronic acid in the deoxygenation.
18. Cost of the organoboron compounds in Sigma Aldrich: Phenylboronic acid 50 g is 73 $; Bis(pinacolato)diboron [$(pinB)_2$] 5g is 101 $; Bis(catecholato)diboron [$(catB)_2$] 5g is 481$; and Tetrahydroxydiboron 5g is 103 $.

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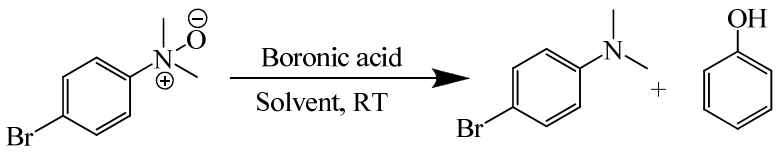
24. The reaction was carried out in acetonitrile due to its buffer miscible properties for conducting UV experiments.

Highlights

1. Deoxygenation of amine *N*-oxides is achieved using the green and economical reagent phenylboronic acid
2. Reaction proceeds under catalyst and metal free conditions
3. Reduction susceptible functional groups are well tolerated
4. Broad substrate scope, clean conversion and excellent yields are the advantages
5. An indirect method for identification and quantification of tert-amine N-oxide is demonstrated using UV-Vis spectrometry

Table 1: Optimization of reaction conditions.[a]

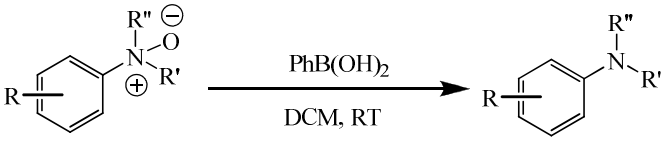


1a **2a** **By-product**

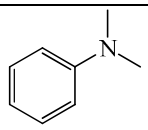
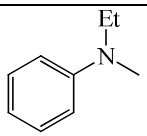
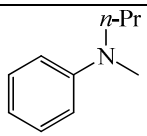
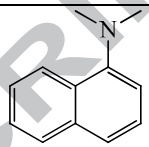
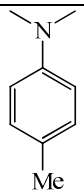
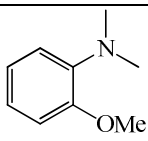
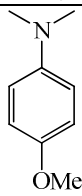
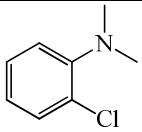
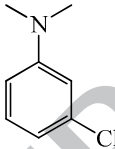
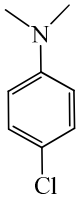
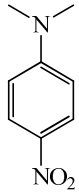
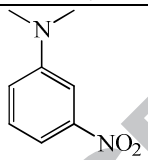
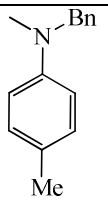
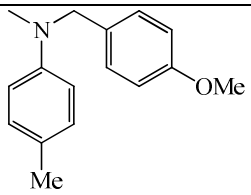
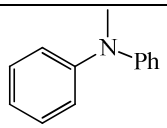
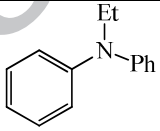
Entry	Solvent	Boronic Acid	Time (mins)	Yield (**2a**) (%)[b]
1	CH_3OH	$PhB(OH)_2$	60	25
2	CH_3OH	$PhB(OH)_2$	12 h	80
3	C_2H_5OH	$PhB(OH)_2$	60	32
4	*t*-BuOH	$PhB(OH)_2$	60	50
5	H_2O	$PhB(OH)_2$	60	30
6	THF	$PhB(OH)_2$	30	89
7	2- Me THF	$PhB(OH)_2$	15	95
8	Toluene	$PhB(OH)_2$	60	46
9	CH_3CN	$PhB(OH)_2$	60	32
10	DCM	$PhB(OH)_2$	5	97
11	DCE	$PhB(OH)_2$	10	97
12	DCM	*p*-Me-$PhB(OH)_2$	5	97
13	DCM	*p*-NO_2-$PhB(OH)_2$	120	94
14	DCM	$MeB(OH)_2$	60	40
15	DCM	n-$BuB(OH)_2$	60	43
16	DCM	$(pinB)_2$[c]	5	97
17	DCM	$(catB)_2$[d]	5	97
18	DCM	$B_2(OH)_4$	5	97

[a]Reaction condition: aniline *N*-oxide (1 mmol) and boronic acid (1 mmol) stirred in different solvents at room temperature. [b]Isolated yield. [c]$(pinB)_2$: bis(pinacolato)diboron. [d]$(catB)_2$: bis(catecholato)diboron.

Table 2: Deoxygenation of *N*,*N*-dialkylaniline *N*-oxides using phenylboronic acid.[a,b]

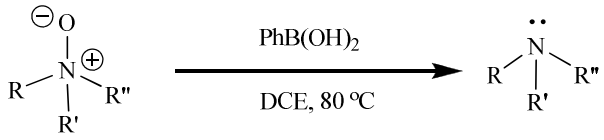


1b-r **2b-r**

 **2b** (5 mins, 98%)	 **2c** (5 mins, 98%)	 **2d** (5 mins, 95%)	 **2e** (10 mins, 96%)
 **2f** (10 mins, 98%)	 **2g** (20 mins, 93%)	 **2h** (20 mins, 92%)	 **2i** (10 mins, 95%)
 **2j** (20 mins, 97%)	 **2k** (10 mins, 97%)	 **2l** (5 mins, 96%)	 **2m** (15 mins, 96%)
 **2n** (15 mins, 97%)	 **2o** (30 mins, 92%)	 **2p** (30 mins, 91%)	 **2q** (20 mins, 93%)
 **2r** (30 mins, 97%)			

[a]Reaction condition: aniline *N*-oxide (1 mmol) and phenylboronic acid (1 mmol) was stirred in dichloromethane at room temperature. [b]Isolated yield.

Table 3: Deoxygenation of trialkyl and benzylamine *N*-oxides with phenylboronic acid.[a,b]

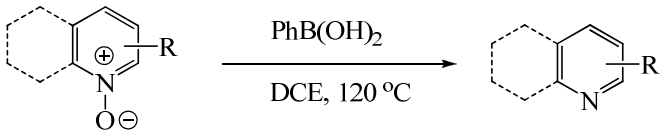


3a-g **4a-g**

4a (12 h, 65%)[c] (30 mins, 93%)	**4b** (30 mins, 92%)	**4c** (45 mins, 90%)
4d (90 mins, 85%)	**4e** (90 mins, 82%)	**4f** (15 mins, 95%)
4g (25 mins, 95%)		

[a]Reaction condition: trialkyl *N*-oxide (1 mmol) and phenylboronic acid (1 mmol) was stirred in dichloroethane at 80 °C. [b]Isolated yield. [c]Reaction was carried out at room temperature.

Table 4: Deoxygenation of heteroaromatic *N*-oxides with phenylboronic acid.[a,b]



5a-h **6a-h**

6a (6 h, 75%)	**6b** (10 h, 90%)	**6c** (24 h, 61%)	**6d** (12 h, 65%)
6e (16 h, 62%)	**6f** (18 h, 60%)	**6g** (8 h, 80%)	**6h** (18 h, 70%)

[a]Reaction condition: *N*-oxide (1 mmol) and phenylboronic acid (1.5 mmol) was stirred in dichloroethane at 120 °C. [b]Isolated yield.

Table 5. Yield comparison between isolated and calculated from UV for the deoxygenation reaction of **1a** with 4-nitrophenylboronic acid.

Entry	Time	UV yield (%)[a]	Isolated yield (%)[b]
1	1h	39	34
2	2h	54	46
3	3h	81	70

[a]Yield was calculated using Beer-Lambert's law (A=Ɛcl) (Refer supporting information). [b]Yield from batch reaction in 1.0 mmol scale.