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Efficient *ipso*-nitration of arylboronic acids with iron nitrate as the nitro source†

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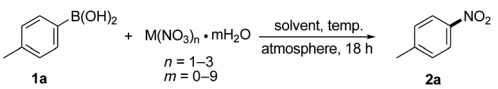
A novel, simple and efficient *ipso*-nitration of arylboronic acids with iron nitrate has been developed. The protocol uses readily available arylboronic acids as the starting materials, inexpensive iron nitrate (0.5 equiv.) as the nitro source without addition of an additive, and the corresponding nitroarenes were obtained in good to excellent yields.

Nitroarenes are key starting materials for the manufacturing of various chemical products,[1,2] such as pharmaceuticals,[3] dyes[4] and materials.[5] The traditional method for the synthesis of nitroarenes is from a mixed-acid (H_2SO_4–HNO_3) strategy. However, isomeric mixtures from the nitration of substituted arenes are often unavoidable, and a weak functional group tolerance is usually observed. In addition, the methods do not meet the requirements of green chemistry because they involve large quantities of hazardous acids. Recently, the efficient transition metal-catalyzed nitrations of aryl halides have been developed.[6] Arylboronic acids and their derivatives are common chemicals, they are easily synthesized from readily available aryl halides and tosylates[7] or by iridium-catalyzed direct borylation of arenes through C–H bond activation,[8] and they have been used as the starting materials to prepare aromatic compounds containing various functional groups.[9] In 2004, Prakash and co-workers reported *ipso*-nitration of arylboronic acids with 2.2 equiv. of $AgNO_3$ or NH_4NO_3 in the presence of 2.2 equiv. of chlorotrimethylsilane,[10] and it seemed that chlorotrimethylsilane was necessary for the reactions. In 2012, Maiti and co-workers developed *ipso*-nitration of arylboronic acids with 2 equiv. of $Bi(NO_3)_3$ in the presence of perdisulfate.[11] Herein, we report a simple, efficient and practical *ipso*-nitration of arylboronic acids with 0.5 equiv. of iron nitrate without addition of any additive.

Initially 4-methylboronic acid (**1a**) was used as the model substrate to screen the reaction conditions, including various nitrate salts, solvents, temperature and atmosphere. As shown in Table 1, nine nitrate salts were tested in toluene at 80 °C

Table 1 *ipso*-Nitration of 4-methylboronic acid (**1a**) with various nitrate salts: optimization of conditions[a]



1a **2a**

Entry	$M(NO_3)_n \cdot mH_2O$ (equiv.)	Solvent	Temp. (°C)	Yield[b] (%)
1	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	Toluene	80	93
2	$Cu(NO_3)_2 \cdot 3H_2O$ (1.5 eq.)	Toluene	80	75
3	$Ni(NO_3)_2 \cdot 6H_2O$ (1.5 eq.)	Toluene	80	20
4	$Mg(NO_3)_2$ (1.5 eq.)	Toluene	80	0
5	$Co(NO_3)_2 \cdot 6H_2O$ (1.5 eq.)	Toluene	80	70
6	$Zn(NO_3)_2 \cdot 6H_2O$ (1.5 eq.)	Toluene	80	10
7	NH_4NO_3 (3 eq.)	Toluene	80	Trace
8	$AgNO_3$ (3 eq.)	Toluene	80	74
9	KNO_3 (3 eq.)	Toluene	80	Trace
10	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	Toluene	80	50[c]
11	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	Toluene	80	40[d]
12	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	CH_3CN	80	20
13	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	*c*-Hexane	80	78
14	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	CH_3OH	80	16
15	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	H_2O	80	0
16	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	Toluene	100	89
17	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	Toluene	60	24
18	$Fe(NO_3)_3 \cdot 9H_2O$ (0.5 eq.)	Toluene	80	92
19	$Fe(NO_3)_3 \cdot 9H_2O$ (0.3 eq.)	Toluene	80	68

[a] *Reaction conditions*: 4-methylboronic acid (**1a**) (1 mmol), solvent (2.0 mL), reaction time (18 h) under nitrogen atmosphere for entries 1–9, 12–19. [b] Isolated yield. [c] Under air. [d] Under oxygen atmosphere. *c*-Hexane = *cyclo*-hexane.

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† Electronic supplementary information (ESI) available: General procedure for synthesis, characterization data, and ^1H and ^{13}C NMR spectra of compounds **3a–v**. See DOI: 10.1039/c3ra45118f

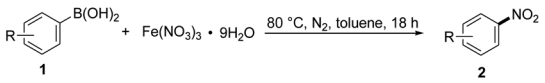
under nitrogen atmosphere (entries 1–9), and $Fe(NO_3)_3\cdot 9H_2O$ afforded the highest yield (entry 1). Lower yields were obtained when the reaction was performed under air (entry 10) or oxygen atmosphere (entry 11). The effect of solvents was investigated (compare entries 1, 12–15), and toluene gave the best result (entry 1). When the reaction temperature was changed (compare entries 1, 16 and 17), the yields were lower than 92% at 80 °C. Interestingly, the yield remained almost unchanged when the amount of $Fe(NO_3)_3\cdot 9H_2O$ was reduced to 0.5 equiv. from 1 equiv. relative to **1a** (entry 18), but it decreased to 68% when the amount of $Fe(NO_3)_3\cdot 9H_2O$ was further reduced (entry 19). Therefore, the optimized conditions for *ipso*-nitration of arylboronic acids can be defined as follows: 1 equiv. of substrate, 0.5 equiv. of $Fe(NO_3)_3\cdot 9H_2O$ as the nitro source, toluene as the solvent at 80 °C under nitrogen atmosphere.

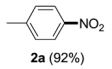
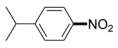
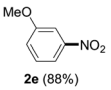
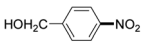
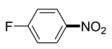
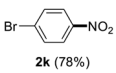
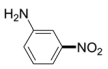
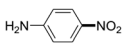
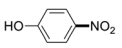
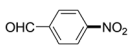
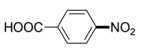
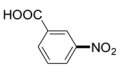
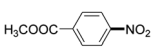
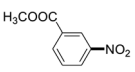
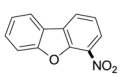
With the optimized conditions for *ipso*-nitration of arylboronic acids in our hands, we then investigated the transformation of a wide range of arylboronic acids to nitroarenes. As shown in Table 2, the examined substrates provided good to excellent yields. The reactivity of arylboronic acids was affected by electronic effects; thus, the substrates containing electron-donating groups provided higher yields than those containing electron-withdrawing groups. Interestingly, also the sterically hindered 2,6-dimethylphenyl-boronic acid (**2c**) gave a high yield. The reactions could tolerate various functional groups in the substrates including ethereal (**2e**), hydroxylic (**2f**, **2n** and **2o**), aminic (**2l** and **2m**), aldehydic (**2p**), carboxylic (**2q** and **2r**), estereal (**2s** and **2t**) functions, as well as carbon–halo bonds (**2h–k**) or an heterocyclic oxygen (**2v**). Therefore, the present method proved of general applicability for the synthesis of diverse nitroarenes.

In order to explore the reaction mechanism, we attempted the reaction of 4-methylboronic acid (**1a**) with $Fe(NO_3)_3\cdot 9H_2O$ in the presence of one equiv. of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) under the above standard reaction conditions (Scheme 1), and only a 12% yield was observed by NMR. This finding is consistent with the possibility that the *ipso*-nitration of arylboronic acids involves a radical process.

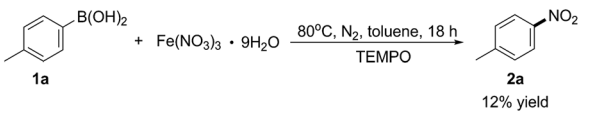
With the aim to further ascertain the existence of a radical mechanism, the reaction of 4-methylboronic acid (one equiv.) with of $Fe(NO_3)_3\cdot 9H_2O$ (0.5 equiv.) in toluene under N_2 was investigated by EPR spectroscopy. As shown in Fig. 1, at room temperature the *g*-factor values of the main signals were 6.3, 4.3 and 2.8 which indicated existence of Fe(III) ion. When the reaction was performed at 80 °C, these signals disappeared to be replaced by a new EPR signal with a *g* value of *ca.* 2.002 from an organic free radical. In this case the EPR experiment, although consistent with a radical mechanism, did not provide valuable information for the identification of the organic radical. The experiment was therefore repeated by examining a narrower magnetic field region centered at the field value corresponding to *g ca.* 2.002 and using a small modulation amplitude the spectrum shown in Fig. 2a was

Table 2 *ipso*-Nitration of arylboronic acids (**1**) with iron nitrate[a]



2 (yield[b])		
 **2a** (92%)	 **2b** (92%)	 **2c** (85%)
 **2d** (89%)	 **2e** (88%)	 **2f** (72%)
 **2g** (68%)	 **2h** (70%)	 **2i** (88%)
 **2j** (87%)	 **2k** (78%)	 **2l** (68%)
 **2m** (60%)	 **2n** (88%)	 **2o** (60%)
 **2p** (74%)	 **2q** (82%)	 **2r** (75%)
 **2s** (86%)	 **2t** (78%)	 **2u** (82%)
	 **2v** (78%)	

[a] *Reaction conditions*: arylboronic acid (**1**) (1.0 mmol), $Fe(NO_3)_3\cdot 9H_2O$ (0.5 mmol), toluene (2.0 mL), reaction temperature (80 °C), reaction time (18 h). [b] Isolated yield.



Scheme 1 Mechanism study on *ipso*-nitration of arylboronic acids with iron nitrate in the presence of TEMPO.

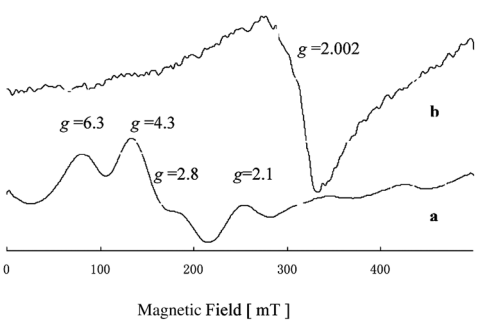


Fig. 1 *In situ* EPR spectra on reaction of one equiv. of 4-methylboronic acid with 0.5 equiv. of $Fe(NO_3)_3$ in toluene under N_2 at room temperature (a) or at 80 °C (b).

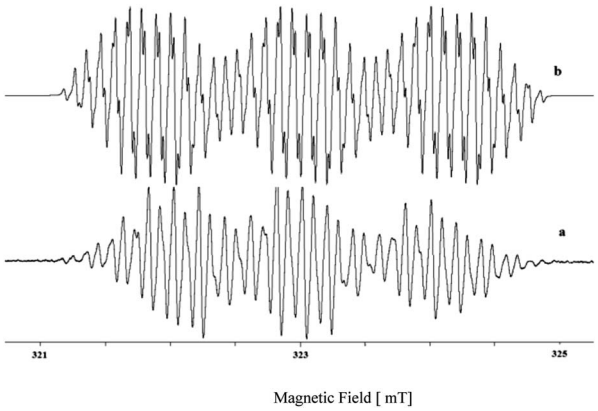
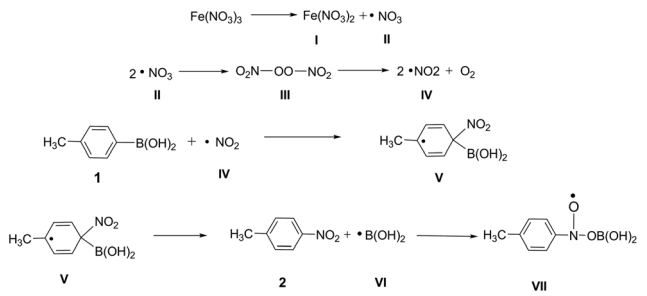


Fig. 2 *In situ* EPR spectra on hyperfine of the free radical for experiment (a) and simulation (b).

obtained. This spectrum was satisfactorily simulated (Fig. 2b) assuming coupling of the unpaired electron with a Boron nucleus, two sets of two equivalent hydrogen atoms, a set of three equivalent hydrogen atoms and a nitrogen atom with coupling constants (see ESI†) typical of a tolyl boroxy nitroxide.

On this basis, a possible mechanism for the *ipso*-nitration of arylboronic acids with iron nitrate is proposed in Scheme 2: accordingly, under heating conditions $Fe(NO_3)_3$ produces $Fe(NO_3)_2$ and the radical NO_3 (**II**) that dimerizes to **III**, which then decomposes to NO_2 (**IV**) releasing oxygen. Radical **IV** reacts with 4-methylphenylboronic acid (**1**) to produce the cyclohexadienyl radical **V** that loses radical $B(OH)_2$ (**VI**) affording the reaction product **2**. Reaction of **VI** with **2** would lead to the detected boroxynitroxide **VII**.

In conclusion, we have developed an easy and efficient *ipso*-nitration of arylboronic acids with iron nitrate. The protocol uses readily available arylboronic acids as the starting materials, 0.5 equiv. of iron nitrate as the nitro source, toluene as the solvent, the reactions are performed under mild conditions without addition of any additive, and the corresponding nitration products are obtained in good to excellent yields. The method could tolerate various functional groups in the substrates and showed a wide generality. Therefore, the present method is amenable to find wide application in various fields.



Scheme 2 Possible mechanism for *ipso*-nitration of arylboronic acids with iron nitrate.

Acknowledgements

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