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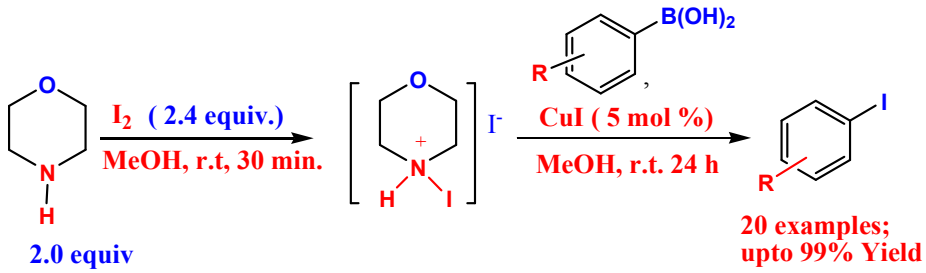
R. H. Tale*[a], G. K. Toradmal, V. B. Gopula



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A Practical and General *Ipso* Iodination of Arylboronic Acids Using *N*–Iodomorpholinium Iodide (NIMI) as a Novel Iodinating Agent: Mild and Regioselective Synthesis of Aryliodides

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R. H. Tale*[a], G. K. Toradmal[a], V. B. Gopula[a]

A mild and efficient protocol for the *ipso*-iodination of aryl boronic acids using N-iodomorpholinium iodide (NIMI) generated insitu from the morpholine and molecular iodine as a novel iodinating agent has been developed. The addition of catalytic amount of copper iodide found to promote rate enhancement of iodination reaction and dramatic increase in the yield depending upon the nature of boronic acid was observed. The mechanistic study revealed that depending upon the nature of substrate, either the classical ipso substitution or copper catalysed iododeborylation pathway overall dominates the present iodination reaction. The features such as mild reaction conditions, operational simplicity, high to excellent yields, excellent functional group compatibility and low catalyst loading makes this method potentially useful in organic synthesis.

Introduction

Development of an efficient, mild and regioselective protocol for the synthesis of aryl halides, in particular aryl iodides is much sought as they are highly versatile synthetic intermediates widely used in transition metal catalyzed carbon-carbon and carbon-heteroatom bonds formation.[1] Aryl iodides are also used as precursors for the synthesis of various hypervalent iodine reagents.[2] Another important utility of iodoarenes is in the area of labeling of biological target with short lived radioisotopes for nuclear imaging by positron emission tomography. For instance, Kim et al.[3] investigated the possibility of using iodine labeled hypericin derivatives for imaging malignant gliomas with PET and SPECT. Moreover, mild and regioselective iodination of arenes is of particular importance from the perspective of iodine labelled diagnostic and therapeutic agents.[4]

Due to the low reactivity of iodine and related iodinating agents than the corresponding chloro and bromo analogues, synthesis of functionalized aryl iodides is more challenging[5]. Generally, iodoarenes are synthesized by the oxidative iodination of arenes with variety of oxidizing agents[6] and using classical Sandmayer reaction[7] involving regioselective iodination of arenediazonium salts under acidic conditions.

However, these methods suffer from the limitations such a use of hazardous oxidizing agents, harsh reaction conditions, poor yields, and regioselectivity. Consequently, many alternative methods for the synthesis of aryl iodides have been developed. These include organocatalytic variants of Sandmayer reaction,[8] the use of mercury[9] and thallium[10] compounds etc., however, these methods also involve the use of toxic reagents. The copper catalyzed synthesis of iodoarenes directly from arenes or aryl bromides as an attractive alternative for the above methods has been reported by Buchwald and co-workers[11].

In contrast to many air–sensitive, tend to be easily hydrolysed organoboron compounds[12], boronic acids [R-B $(OH)_2$], are usually crystalline solids, stable to air and moisture and are relatively of low toxicity [benzene boronic acid: [13] LD_{50}, oral-rat = 740 mg/kg] and environmental impact. Apart from being versatile building blocks in organic synthesis, boronic acids find numerous applications such as in the field of material science, biotechnology, medicinal chemistry and supramolecular chemistry[14]. The recent advancement in the transition metal catalyzed Miyaura borylation[15] and Irridium catalysed C-H activation strategies[16], the large number of boronic acids could be readily synthesized without using haloarenes, an unaccclaimed perception among scientific community, has advance the field of organoboron chemistry further.

In recent years, *ipso* substitution of organoboron compounds, in particular, of arylboronic acids,/esters/trifluorobortae, in which boronic or related group is replaced by entering functional group has emerged as powerful tool for the regioselective functionalization of arenes. This strategy has

[a]School of Chemical Sciences, S.R.T.M. University, Nanded-431606, India.

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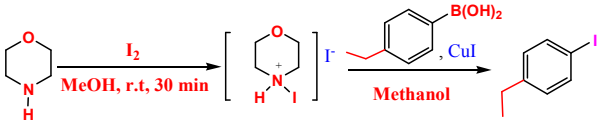
been successfully employed for the synthesis of arylazides,[17] phenols,[17a,18] arylsulfones,[17a,19] aryl halides,[17a,20,21] nitroarenes [17a,22] and amines [17a,23]. Based on similar strategy, very recently, we have reported an efficient and green protocol for the ipso iodination of arylboronic acids using CTAB/I_2 in aqueous media.[24] As compared to other *ipso* substitutions (*ipso* nitration, azidation, hydroxylation and amination), relatively the reports on the ipso iodination of arylboronic acids are scares. Moreover, many reported methods for the ipso iodination in the literature[17a, 19a,f,24] are either performed at high temperature or required large excess of additives/special ligand and high catalyst loading and some of them are having limited substrate scope.[24] Therefore, the general, milder and inexpensive alternative is highly desired.

The guiding principle of ipso substitution is that it generally requires the concomitant activation of both the organoboron compounds (via Lewis acid-base type interaction) and electrophilic species (for instance, iodinating agents) which help ipso substitution to occur readily. We reasoned that the activation of I_2 with mild base such as morpholine at room temperature would generate insitu N-iodomorpholinium iodide (NIMI). The activation of boronic acid by iodide (I-) ion giving more nucleophilic boron species and its subsequent ipso attack with highly electrophilic N-iodomorpholinium ion could lead to the mild and efficient protocol for ipso iodination of boronic acids at room temperature.

In the present paper, in continuation of our interest in exploring boronic acids as green catalysts or reagents in organic synthesis[24,25] we report herein the copper catalysed an efficient, mild, and general approach for the regioselective synthesis of iodoarenes via ipso iodination of boronic acids using N-iodomorpholinium iodide as iodinating agent at low catalyst loading.

Results and Discussion

The iodinating agent used here, *N*-iodomorpholinium iodide[26] was generated *insitu* from I_2 and Morpholine using initially, the *ipso* iodination of 4-ethylphenyl boronic acid using morpholine and I_2 in methanol was considered as a model reaction. A series of experiments were carried to optimize various parameters such as effect of morpholine: I_2 ratio, catalyst loading, temperature, solvent and reaction time (scheme-1).



Scheme-1

The results are summarized in table-1. As can be seen from our results, in the absence of morpholine and using I_2 alone , the reaction hardly proceeded despite of continuing the reaction for 24 h at room temperature, (table-1, and entry-1) and use of even higher temperature did not facilitate the reaction (table-1, entry-2). However, the using stoichiometric amount of morpholine and little excess of I_2, the above reaction proceeded smoothly but to give low yield, (table 1, entry 3). In order to improve the product yield, we decided to probe the effect of copper catalyst on this reaction. Thus using catalytic amount (5 mol %) of CuI, considerable increase in the yield of the above reaction was observed (table-1, entries 3 vs 4). Under same reaction conditions but using higher temperature, a good yield of corresponding iodoproduct could be obtained within short reaction time (table-1, entry-5). Use of equimolar amount of morpholine to I_2 did not give much favorable result even in the 10 mol% of the catalyst. On the other hand, using 1:2.4 equiv. of morpholine and I_2 and in the presence of 10 mol % of catalyst, 68% yield was obtained at 40^{0}C within 24 h.

Table-1 Optimising the reaction conditions for the *ipso* iodination of 4-ethylphenyl boronic acid[a]

Entry	Morpholine (equiv.)	I_2 (equiv.)	CuI (mol %)	Temp. (^{0}C)	Time (h)	Yield (%)[b]
1	None	1.2	None	rt	24	0
2	None	1.2	None	65	10	Trace
3	1.0	1.2	none	rt	24	32
4	1.0	1.2	5	rt	24	40
5	1.0	1.2	5	65	10	68
6	1.0	1.0	10	65	4	39
7	1.0	2.4	10	40	24	68
8	1.0	2.4	5	65	4	50
9	2.0	2.4	None	rt	24	67
10	2.0	2.4	5	rt	24	75
11	2.0	2.4	5	65	4	74
12	2.0	2.4	5	rt	24	62[c]
13	2.0	2.4	100	rt	1	65
14	0.2	1.0	None	40	24	12
15	0.2	2.4	None	40	24	28
16	0.2	2.4	5	40	24	30
17	None	2.4	5	40	24	29
18	None	None	100	rt	5	nd[d]
19	None	None	5	rt	24	0[e]

[a] Reaction conditions: 0.2 mmol of 4-ethylphenyl boronic acid in 1.5 ml of methanol for the time indicated in table. [b] Isolate yields by column chromatography. [c] Under N_2 atmosphere. [d] The boronic acid was completely consumed but no iodoproduct was detected. [e] 2.0 equiv. of KI or NaI was used as iodinating agent.

Despite of several attempts, the yield was still not as good as the process to be called practical. Therefore, to improve the yield further, we decided to use further higher amount morpholine and iodine. We were delighted to see that using

twofold amount of these above reagents, more than two fold increases in the yield was observed, (table-1, entry 3 vs 9). In the presence of catalytic amount of copper iodide, however, the same reaction furnished 75 % yield of the corresponding iodoproduct, (table-1, and entry-10). Almost similar result was obtained when above reaction was performed at 65^0C but within short reaction time (table-1, entry-10 vs 11). These results clearly indicate the striking effect of temperature on the present iodination reaction. Use of inert (N_2) atmosphere found to be detrimental for the present reaction as it gave less favourable result, (table-1, compare entries 11 and 12). As anticipated, using stoichiometric amount of copper catalyst, reaction reached to completion within less than hour but wi6th lower yield even than the uncatalyzed reaction (Table 1, compare entries-9 and13).

To check whether the reaction can be proceeded even using catalytic amount of morpholine, the model reaction was performed again but this time using catalytic amount of morpholine. As can be seen from our results that the use of catalytic amount morpholine and little excess of I_2 could promote the *ipso* iodination but to give very low yield, (table-1, entry-14). Use of twofold excess of I_2, however, resulted into more than twofold increase in the yield under same reaction conditions (table 1, entry-15). We also checked the effect of catalytic amount of morpholine and CuI in the model reaction. Unfortunately, under thes conditions the reaction furnished very low yield of the iodoproduct. Thus the use of catalytic amount morpholine alone or in combination with CuI did not provide the acceptable results and hence no further attempts of optimizing the catalytic study were made.

Also to check whether the CuI alone or CuI/I_2 system could facilitate the *ipso* iodination of boronic acid, two independent experiments were carried out. One involving copper iodide alone and another one involving catalytic CuI and excess of I_2.. While CuI/I_2 as an iodinating agent found to facilitate the ipso iodination albeit in low yield (tabl-1, entry -16), the use of CuI alone did not give any ipso product even in the presence of stoichiometric amount of former. (table-1 entry-17). Finally, the use of alternative iodinating agents such as KI and NaI did not furnish any *ipso* product (table-1 entry-18). Thus 2:2.4 equiv. of morpholine to I_2 ratio was found to be optimal for the success of the reaction.

We also investigated the effect of different copper salts such as CuCl, CuCN, $Cu(OAc)_2$, $CuSO_4$, and CuO on model reaction using optimized reaction conditions as described above (table-1,entry-10).The results are summarised in table-2.

Table-2 Effect of copper salts on the *ipso* iodination of 4-ethylphenylboronic acid[a]

Entry	Copper Salt	Yield (%)[b]
1	None	67
2	CuI	75
3	CuCl	71
4	CuCN	72
5	$Cu(OAc)_2$	65
6	$CuSO_4.5H_2O$	55
7	Cu_2O	71

[a] Reaction conditions: 0.2 mmol of 4-ethylphenyl boronic acid, 0.4 mmol of morpholine, 0.48 mmol of I_2 in the presence of 5 mol% of Copper salt in 1.5 ml of methanol at room temperature for 24h. [b] Isolated yield by column chromatography.

Among various copper salts screened, CuI was found to be the most effective catalyst giving highest yield of the iodoproduct (table-2, entry-2). The copper salts such as CuCl (table-2, entry-3), CuCN (table-2, entry-4) and CuO (table-2, entry-7) were also found to be effective catalysts, however they furnished lower yields as compared to CuI under same reaction conditions. The other catalysts such as $CuSO_4$ and $Cu(OAc)_2$ found to have no effect on the iodination reaction as they furnished lower yields even than the uncatalyzed reaction (table-2, compare entries-1, 5 & 6). The reactions involving these two copper salts resulted into relatively complex reaction mixture as compared to other catalysts which probably might be reason behind the low yields obtained using them.

Initially, the methanol was deliberately chosen as a solvent due to high solubility of the salt, *N*-iodomorpholinium iodide in methanol.[26] We also investigated the effect of various solvents such as DCM, acetonitrile, acetone, DMF and THF on the model reaction.

The results are shown in table-3. As can be seen from our results, amongst all the solvent tested, the methanol was found to be best solvent (table-3, entry-1). The DCM was found to be another effective solvent for the present reaction but gave little lower yield than methanol (table-3, entry-2). The acetonitrile (table-3, entry-3) and DMF (table-3, entry-4) furnished moderate and low yield respectively and thus proved to be less effective solvents than methanol and DCM. Acetone (table-3, entry-5) on the other hand found to be fruitless solvent for the present reaction giving only 5% yield. Finally, THF was found to have detrimental effect on the reaction as it gave complex reaction mixture, though the starting material was found to be completely consumed as indicated by TLC (table-3, entry-6).

Table-3 Effect of solvent on *ipso* iodination of 4-ethylphenyl boronic acida

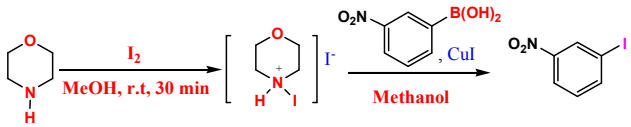
Entry	Solvent	Yield (%)[b]
1	MeOH	75
2	DCM	72
3	MeCN	58
4	DMF	36
5	Acetone	5
6	THF	---[c]

[a] Reaction conditions: 0.2 mmol of 4-ethylphenyl boronic acid, 0.4 mmol of morpholine, 0.48 mmol of I_2 in the presence of 5 mol% of CuI in 1.5 ml of methanol at room temperature for 24h. [b] Isolated yields by column chromatography. [c] A complex reaction mixture was formed

From the detail optimization study, it was found that the CuI had little effect on the present iodination reaction. The other

catalysts found to have either lower effect that CuI or less effective even than uncatalyzed reaction. Thus, initial study could not provide the clear information as to the exact role of copper catalyst in the reaction.

In order to have the clear insight into the role of the copper catalyst, solvent effect and reaction conditions on the ipso iodination reaction, we thought it is worthwhile to have the optimization study with the electron deficient substrate. To probe the effect of above parameters on the iodination reaction, this time the *ipso* iodination of 3-nitrophenylboronic acid was considered as model reaction, scheme-2.



Scheme-2

The results are summaries in table-4.

Table-4 Optimising the reaction conditions for the *ipso* iodination of 3-nitrophenyl boronic acid[a]

Entry	Morpholine (equiv)	I_2 (equiv.)	CuI (mol%)	Temp. (^{0}C)	Time (h)	Yield (%)[b]
1	0.2	2.4	5	Rt	24	21
2	0.2	2.4	5	40	24	26
3	2.0	2.4	None	Rt	24	20
4	2.0	2.4	None	40	24	41
5	1.0	2.4	5.0	40	24	63
6	2.0	2.0	5.0	65	4	92
7	2.0	2.4	5.0	Rt	24	94
8	2.0	2.4	5.0	40	24	>99[c]
9	None	2.4	5.0	40	24	15.

[a] Reaction conditions: 0.2 mmol of 3-nitrophenyl boronic acid in 1.5 ml of methanol for the time indicated in table. [b] Isolate yields by column chromatography. [c] reaction time was not optimised and reaction was continued for 24 h.

As shown in table-4, reaction can be proceded using catalytic amount of morpholine to give 21 and 26 % yield of the iodoproduct at room temperature and 40^{0}C respectively. (table-4, entries-1 and 2). To our surprise, however, using 2:2.4 equiv. of morpholine to I_2 ratio but without copper catalyst, the reaction gave only 20 % yield of the corresponding iodoproduct at room temperature. Thus in contrast to the results obtained with 4-ethylphenylboronic acid, the significant effect of copper catalyst on the ipso iodination of 3-nitrobenzeneboronic acid could be observed even at catalytic level of morpholine (table-4, compare entries-1 and 3). Interestingly, using 1:2.4 equiv. of morpholine to I_2 ratio and 5 mol % of CuI, 64% yield (table-4, entry-5) of the corresponding iodoproduct was obtained. This result is much closer to the yield obtained with 4-ethylphenylboornic acid when 10 mol % of CuI was used (compare table-1, entry-7 with table-4, entry-5). Furthermore, using stoichiometric amount of morpholine and I_2, but at higher temperature, the reaction reached to completion rapidly to give 92 % yield which is much greater than the yield obtained with 4-ethylphenylboronic acid but using 2:2.4 equiv. of morpholine and I_2 ratio under almost similar conditions. (Compare table-1, entry-11 with table-4 entry-6). To our delight, using 2:2.4 equiv. morpholine and I_2 ratio and 5 mol % of CuI, excellent and almost quantitative yield of the 3-nitrio-1-iodobenzene were obtained at room temperature and 40^{0}C respectively All these findings clearly indicates the pronounced effect of copper iodide on the iodination of 3-nitrophenylboronic acid as compared to the 4-ethylphenylboronic acid. Surprisingly, in the absence of morpholine but using CuI/I_2 as iodinating agent, much lower yield than that of 4-ethylboronic acid was obtained under exactly same reaction conditions.(compare table-1, entry- 15 with table-4, entry-9).The above results clearly indicates the crucial role of morpholine in the present iodination reaction.

It's worth mentioning here that with electron 4-ethylphenylboronic acid only 10 % increment in the yield while in case of electron deficient 3-nitophenylboronic acid dramatic increment in the yield (94 % vs 20 mol %) in copper catalysed reaction as compared to the catalyst free reaction was observed, (table-1,entries-6 and 7 vs table-4, entries-2 and 6). Explicitly, present iodination reaction is strongly dependence upon the electronic nature of the substituent. It can be concluded that the copper catalyst has little effect on the ipso iodination of electron rich substrate but at the same time it dramatically accelerates the reaction when electron withdrawing substituent is present in the boronic acid.

Similar to 4-ethylphenylboronic acid, we also investigated the effect of different copper salts and solvents on the model reaction in this case also. The results are summarized in table-5. As can be seen from our results, CuI and CuCl (table-5, entries-2 and 3) were found to be equally effective catalysts giving near quantitative yield of the corresponding iodoproduct under optimized reaction conditions. In contrast to the results obtained with 4-ethylphentlboronic acid, all the copper salts screened here shown pronounced catalytic effect on the present iodination reaction as compared to the uncatalyzed one giving high to near quantitative yield of the corresponding iodoproduct.

Table-5 Effect of different solvents and copper salts on *ipso* iodination of 3-nitrophenylboronic acid[a]

Entry	Solvent	Copper Salt (CuX)	Yield (%)[b]
1	MeOH	CuI	>99
2	MeOH	CuCl	99
3	MeOH	Cu_2O	80
4	MeOH	$CuSO4.H_2O$	94
5	MeOH	$Cu(OAc)_2$	89
6	DCM	CuI	10
7	MeCN	CuI	59
8	DMF	CuI	Trace
9	Acetone	CuI	6

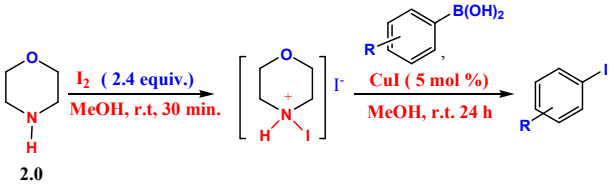
[a] Reaction conditions: 0.2 mmol of 3-nitrolphenyl boronic acid, 0.4 mmol of morpholine, 0.48 mmol of I_2 in the presence of 5 mol% of CuX in 1.5 ml of solvent at 40^{0}C for 24h. [b] Isolated yields by column chromatography

In sharp contrast, the copper salts, $Cu(OAc)_2$ and $CuSO4.H_2O$ which were found to be less effective catalysts even than uncatalyzed reaction in case of 4-ethylphenylboronic acid, proved to be highly effective catalysts for iodination of 3-nitophenylboronic acid giving very high and excellent yield respectively (table-5, entries-4 and 5).

Next the effect of all the solvents investigated previously also tested here. Once again, methanol found to be the best solvent giving highest yield among all the solvent tested. However, the DCM, acetonitrile, and DMF which were proved to be the effective solvents in earlier study, in the present case, except acetonitrile, they found to be fruitless solvents giving very low or poor yield.

Thus the CuI and methanol were found to be most suitable catalyst and solvent respectively for the substrates, 4-ethyl and 3-nitrophenylboronic acid. It's worth mentioning here that the reaction parameters such as nature of copper catalyst, catalyst loading, and morpholine: I_2 ratio, temperature and solvent all have strikingly different effect on the ipso iodination of electronically contrasting substrates.

The ipso iodination of both, 4-ethyl and 3-nitobenzeneboronic acid can be proceeded very rapidly with good and excellent yields respectively but at the expense of high catalyst loading and temperature, (table-1, entry-11 and table 4 entry-8). However, without necessarily relying on such a drastic conditions, excellent results could be obtained using low catalyst loading and under mild conditions. Thus 1.0 equiv. of boronic acid, 2.0 equiv. morpholine, and 2.4 equiv. of I_2 in the presence of 5 mol % CuI in methanol at room temperature for 24 h were considered to be the best reaction conditions and used for further study (scheme-3).

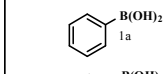
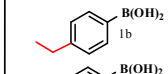
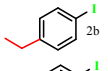
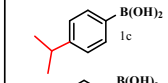
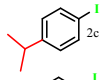
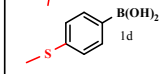
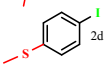
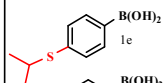
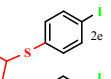
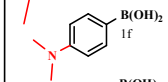
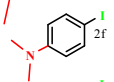
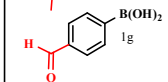
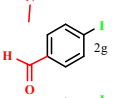
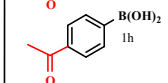
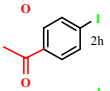
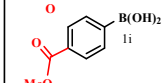
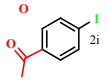
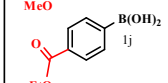
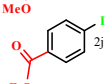
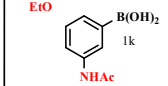
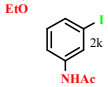
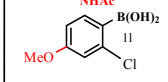
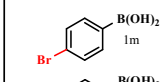
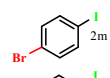
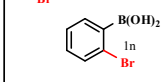
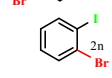
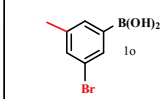
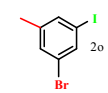
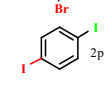
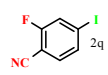
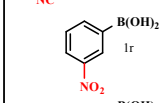
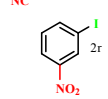
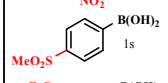
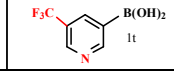


Scheme-3

With optimized reaction conditions at hand, next the scope and generality of the reaction was explored using diverse arylboronic acids. The results are summarized in table-6. As can be seen from our results, the reaction is general as the structurally diverse boronic acids reacted smoothly under present reaction conditions giving well to excellent yields of the corresponding aryliodides[27]. Though electron neutral phenylboronic acid provided moderate yield (~39%) of the iodoproduct, (table-6, enty-1), the electron rich and electron deficient boronic acids invariably shown much higher reactivity under optimized conditions as described previously.

The arylboronic acids bearing alkyl-, (table-6, entries-2 and 3), alkylthio- (table-6, entries-4, and 5), carbonyl- (table-6, entry-7

Table-6 Scope of boronic acids in copper catalysed *ipso* iodination[a]

Entry	Boronic acid	Product	Yield (%)[b]
1			39
2			75
3			90
4			87
5			95
6			---[c]
7			85
8			53
9			82
10			92
11			85
12			93
13			90
14			78
15			96
16			95
17			81
18			94
19			83
20			28

[a] Reaction conditions: 0.2 mmol of boronic acid, (0.4 mmol) of morpholine, 0.48 mmol of I_2 in the presence of CuI (5 mol %) in methanol (1.5 ml) at room temperature for 24h. [b] Isolated yields by column chromatography [c] A complex mixture was obtained.

and 8), alkoxy- (table-6, entry-12), alkoxycarbonyl- (table-6, entries 9 & 10), amide- (table-6 entry-11), halide- (table-6, entries-12,13,14,15 and 16), cyano- (table-6, entry-17), nitro- (table-6, entry-18), sulfonyl- (table-6-entry-19) etc. participated successfully in the *ipso* iodination process. Notably, one of the most electron deficient boronic acids, for instance, 3-nitrobenzeneboronic acid had shown exceptionally high reactivity giving near quantitative yield of the iodoproduct using these conditions

Of particular importance, ortho substituted, sterically hindered boronic acids such as 2-chloro-4-methoxy-(table-6, entry-12) and 2-bromophenylboronic acid (table-6, entry-14) also found to be the suitable substrates in the present reaction giving excellent and good yield of the corresponding iodoproducts respectively.

The representative heteroarylboronic acids such pyridine-4 boronic acid and 5-trifluomethyl-pyridin-3-boronic acid were also investigate under present reaction conditions. The corresponding 3-Iodo-5-trifluomethyl-pyridin was obtained in 28 % yield (table-6, entry-20) and unfortunately, the isolation of product from the reaction of pyridine-4-boronic acid by column chromatography was almost become impossible probably due to rapid formation of corresponding *N*-oxide and other side products (result not shown). The low yield in case of 5-trifluomethyl-pyridin-3-boronic acid was mainly due to the complications arised during column chromatography (despite of using triethyl amine treated silica) as TLC indicated complete consumption of starting material. For similar reason, highly electron rich, (4-*N, N*-dimethylamino) phenyl boronic acid (table-6, entry-6) failed to furnish any *ipso* product.

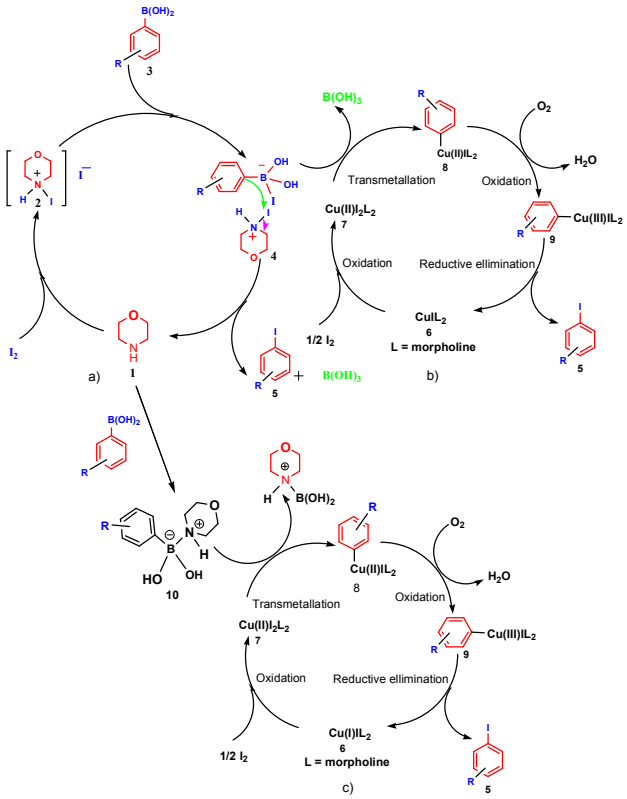
Its worth mentioning here that very recently we reported the green protocol for the ipso iodination of aryboronic acids using CTAB/I_2 in aqueous media. Though the method provides the green alternative for the synthesis of aryl iodides, however, it required high temperature (80^0C) and has limited substrate scope as only electron rich boronic acids were found to be the suitable substrates. As compared to our previous work, the present method involving novel NIMI as iodinating agent is highly versatile as both electron rich as well as electron deficient arylboronic acids and hetroarylboronic acids reacted efficiently to give good to excellent yield of the aryliodides. Furthermore, the method is mild, operationally simple and could be carried out in open atmosphere without the need for special ligand or additives using very low catalyst loading. Thus these two methods have significant differences and the present method provides alternative ipso iodination tool for synthetic applications.

As alkylboronic acids such as methyl- and indanylboronic acids (results not shown) did not react at all under present reaction conditions, it was clear that the presence of aryl group was the prerequisite for the success of the iodination reaction. In general, the reaction was highly regioselective and invariably no formation of other side products was observed.

Finally, we sought to determine the plausible mechanism(s) for the present ipso iodination process. Regarding mechanistic aspect of the present reaction, we carefully noted many crucial facts during our optimization study: 1) the reaction can be proceeded using catalytic amount of morpholine (table-1, entries-2 and 3 and table-4, entries-1and 2) indicates that morpholine might be regenerated during the catalytic cycle, 2) the iodination does not proceed at all even using stoichiometric amount of CuI or more than twofold excess of I_2 alone, but using catalytic amount of CuI and excess I_2 the ipso iodination proceeded smoothly even at room temperature. We believe that that I_2 oxidizes CuI to copper (II) species which must acts as a true catalyst 3) there is little effect of CuI on the reaction with 4-ethylphenylboronic acid but the effect is pronounced in case of electron deficient 3-nitrophenylboronic acid indicates that CuI plays pivotal role in the catalysis of iodination of 3-nitrophenylboronic acid and related substrates. 4) under inert atmosphere, the yield obtained was more or less similar to that of uncatalyzed reaction (table-1, entry 15 vs 10) justifying the need for air atmosphere to facilitate the copper catalysed pathway and 5) the fact that in the absence of morpholine but using CuI and I_2 very low yield was obtained (table-1, entry 15 vs 17) and using other iodinating agents such as KI or NaI, the reaction did not proceed at all even in the presence of stoichiometric amount of CuI evident the key role of NIMI for the success of the reaction.

6) The transmetallation of organoboron compound to organocopper is not a general reaction. Due to their similar bond energies and electronegativities such a transmetalation of organoboron to organocopper reagents is limited to the preparation of alkenylcopper and to some extent to unfunctionalized alkylcopper compounds.[28] This is why the popular Chan-Lam coupling requires either stoichiometric copper catalyst or catalytic copper strictly under oxygen atmosphere or other primary oxidant in the presence of 2-3 equivalent of amine base and special ligand. In case of 3-nitrophenylboronic acid the use of excess morpholine can only proceed the reaction successfully. Therefore, we believe that in the present CuI catalysis such a transmetallation of 3-nitrophenylboronic acid other electron deficient substrates to the corresponding organocopper reagent must be a slow process and the use of excess morpholine must compensate for the same ultimately giving satisfactory result.

All these findings lead us to speculate that the present ipso iodination reaction can be attributed to the multiple underlying mechanisms such as concomitant metal free ipso-iodination and **NIMI/**morpholine assisted copper-catalyzed deiodoborylation pathway and depending upon the nature of substrate either of them overall dominates the reaction. On this basis, we proposed the plausible mechanism(s) for the ipso iodination of the boronic acid as outline in Scheme-4.



Scheme-4. Proposed mechanism(s) for the ipso iodination of boronic acid: (a) classical ipso-iodination pathway and, (b) and (c) **NIMI** and Morpholine assisted copper-catalysed deiodoborylation pathways respectively.

The N-iodomorpholinium iodide **2** generated from morpholine **1** and I_2 acts as actual iodinating agent. The iodide ion activates the boronic acid **3** via Lewis acid-base type interaction leading to the formation of ionic species **4**. The ipso attack involving N-iodomorpholinium ion lead to the formation of iodocompound **5** and morpholine is regenerated and reused again. As regard to the copper catalysed deiodoborylation pathway, we believe that the oxidation of CuI **6** with I_2 generates Cu (II) species **7** which supposed to be the actual copper catalyst. The transmetallation between **7** and **4** form the organocuprate **8** which on air oxidation or oxidation with equilibrated O_2 in methanol[29] results into the formation of aryl copper (III) intermediate **9**. The reductive elimination of **9** yield the aryliodides **5** and Cu (I) species is regenerated and reused again. Alternatively, the improvement of the yield in correlation to the added morpholine can also be explained on the basis of participation of morpholine-boronic acid "ate complex" **10** in copper catalysed deiodoborylation pathway **(Scheme-4**, path C **).** This also strongly suppor the need for excess morpholine for the smooth proceeding of the reaction. However, the possibility of stabilization of unstable CuI_2 by morpholine as a ligand cannot be ruled out at this point of time

Experimental Section

General information

All the solvents were redistilled before used. Analytical TLCs were performed on Merck silica gel 60F254 plates. The boronic acids were purchased from Johnson Matthey Chem. Ltd. and other chemicals were purchased from Sigma Aldrich Chem. Ltd. The IR spectra (ATR mode.) were recorded on Brucker IR spectrometer. The ^{1}H and ^{13}C NMR spectra (in CDCl3) were recorded on Agilent 400 or Bruker Avance-II 400 MHz spectrometer. The Chemical shift values are on a δ scale and TMS was used as an internal standard. The ^{19}F NMR spectra were recorded in DMSO-d6 on Bruker Avance II 400 MHz spectrometer using $CFCl_3$ as internal standard. Abbreviations used are: s (singlet), d (doublet), t (triplet), dd (double doublet), dt (doublet triplet), m (multiplet). The high-resolution mass spectral analysis was performed on Micromass Q-Tof (ESI-HRMS) and GCMS were ecorded on Shimadzu gas chromatograph.

General procedure for the synthesis of aryl iodides

To a 10 ml round bottomed flask charged with morpholine (0.4 mmol, 2 equiv.) and I_2 (0.48 mmol, 2.4 equiv.) was added methanol (1.5 ml) and the reaction mixture was stirred for 30 minutes at room temperature. Then the appropriate arylboronic acid (0.2 mmol) and CuI (2 mg, 0.01 mmol) was added to it and the mixture was stirred vigorously at room temperature for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with 10 % sodium thiosulphate solution (to remove excess of iodine) and extracted with ethyl acetate (3* 10 ml) and the combined organic extract was washed with water and brine. The evaporation of solvent under vaccu after drying over anhy. Na_2SO_4 followed by column chromatography (petroleum ether (100 %) or petroleum ether: ethyl acetate, 9:1) gave the analytically pure product. (Note: direct column chromatography of crude product adsorbed on silica followed by washing the effluent with Na_2SO_4 solution, drying and evaporation of residue gave exactly similar results).

Conclusions

In conclusion, we have developed the general and efficient protocol for the regioselective synthesis of aryl iodides via *ipso*-iodination of arylboronic acids using N-iodomorpholinium iodide as iodinating agent under mild conditions. The method utilizes the readily accessible and cheap reagents, morpholine & $I_{2,,}$ copper iodide as catalyst, nonhazardous methanol as a solvent and could be performed in open atmosphere without the need for any special ligand or additives. The mild reaction conditions, operational simplicity, high to excellent yields, excellent functional group compatibility and low catalyst loading are the noteworthy features of the present method which makes it an attractive alternative for the synthesis of valuable aryl iodides. The present method would attract much attention of chemical community at large.

Acknowledgements

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27 The analytical data for representative compounds are provided below:
4-Ethyliodobenzene 2b: Yellow liquid, 75% 1HNMR: δ 1.20 (t, 3H), 2.57 (q, 2H), 6.93-6.95 (dd, 2H), 7.57-7.59 (dd, H). EI-MS $[M]^+$ = 232
4-Isopropyl iodobenzene 2c: Yellow liquid, 90% 1HNMR: (CDCl3, 400 MHz) δ 1.25 (d, 6H), 2.68 (septet, 1H), 6.98-7.00 (dd, 2H), 7.61-7.63 (dd, H); EI-MS $[M]^+$ = 246
Isopropyl-4-iodophenyl sulphide 2e: Yellow liquid, Yield 95% 1HNMR (CDCl3, 400 MHz): δ 1.27 (d, 6H), 3.35 (septet, 1H), 7.10-7.12 (dd, 2H), 7.58-7.60 (dd, H). 13 NMR (CDCl3, 400 MHz): δ 23.00, 36.1, 91.7, 133.2, 135.7, 137.7; GC-MS RT= 11.01[m/e] = 278
4-Carboethoxyiodobenzene 2j: Yellow liquid, Yield 92 % 1HNMR (CDCl3, 400 MHz): δ 1.38 (t, 3H), 4.35 (q, 2H), 7.73-7.76 (m, 2H), 7.78-7.81 (m, 2H). 13C NMR (CDCl3, 400 MHz): δ 14.5, 61.2, 100.6, 129.9, 131, 137.6, 166
2-Chloro-1-iodo-4-methoxybenzene 2l: Faint Yellow oil, Yield 93 % 1HNMR (CDCl3, 400 MHz): δ 3.78 (s, 3H), 6.55 (dd, J= 2.97 Hz, 1H), 7.02 (dd, J= 2.68 Hz, 1H), 7.67 (t, J= 8.78 Hz, 1H). EI-MS: m/z $[M+H]^+$ = 268.8
1-Bromo-3-iodo-5-methylbenzene 2o: Light Yellow liquid, Yield 96 % 1HNMR (CDCl3, 400 MHz): δ 2.28 (s, 3H), 7.29 (s, J= 71.21 Hz, 1H), 7.46 (s, J= 75.60 Hz, 1H), 7.65 (s, 1H). EI-MS: m/z $[M+H]^+$= 297.9
4-Iodophenylmethyl sulfoxide 2s: While solid, Yield 83 % 1HNMR (CDCl3, 400 MHz): δ 3.03 (s, 3H), 7.63-7.65 (m 2H), 7.91-7.93 (m, 2H), 13C NMR (CDCl3, 400 MHz): δ 44.4, 101.6, 128.7, 138.6, 140.1
3-(trifluoromethyl)-5-iodopyridine 2t: White Solid, Yield 28 % (isolated by column chromatography using trimethyl amine pretreated silca gel) 1HNMR (CDCl3, 400 MHz): δ 8.24-8.25 (m 1H), 8.83 (s, 1H), 9.03 (s, 1H), HRMS (Calculated for C6H3NIH= 272.9271); Found = 273.9341 $(M+H)^+$

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