FREE METAL EFFICIENT PHOTOCHEMICAL BORYLATION OF ARYL HALIDES IN THE DIFFERENT CONDITIONS

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abstract

A rate, chemoselective and metal-free C–B bond-forming reaction of aryl iodides and bromides in liquid solution at low temperatures was discovered. This reaction is amenable to batch and continuous-flow conditions and exhibites exceptional functional group bearing and broad substrate range of regarding both the aryl halide and the borylating reagent. previous mechanistic experiments shows a photolytically generated aryl radical as the key intermediate.

Keyword: *borylation, aryl halides*

Introduction

Arylboronic acids and esters have found wide applications in chemical, medicinal and materials sciences. In synthetic organic chemistry, specific, they are versatile synthons for the building of carbon–carbon or carbon–heteroatom bonds.1 Conventional methods for generating arylboron compounds to include reactions of arylmetallic intermediates with trialkyl borates, to pursue by transesterification or hydrolysis. These reactions suffer some major drawbacks such as limited functional group tolerance as well as the necessity of rigorous anhydrous conditions (Scheme 1a).2 In recent decades, transition metal-catalyzed borylation reactions using palladium, nickel, copper and zinc have to appear as highly useful methods for to change of C–X bonds to C–B bonds (Scheme 1b).3

In recently, direct C–H borylation methods based on transition-metal catalysts have also been developed.4 In order to decrease the costs and the amount of heavy metal residue in the final products, a few transition-metal-free methods for C–B bond formation have been developed. Ito and coworkers discovered an alkali alkoxide-mediated borylation of aryl halides with a silylborane as the unique borylating reagent (Scheme 1c).5 Zhang and coworkers reported that aryl iodides could be borylated with 4.0 equivalents of bis(pinacolato) diboron in refluxing methanol using 2.0 equivalents Ce2CO3 as the promoter.The reaction time ranged from several hours to days and the yields were generally moderate (Scheme 1d).6

Fernandes´ and Muniz˜ transformed diaryliodonium acetates to arylboronates under moderate conditions.7 Using aryl amines as the starting material, Wang developed a mild and efficient Sandc meyer-type borylation process.8a–c Borylation of aryl diazonium salts8d–f and aryl triazenes8g has also been reported. In addition, new methods for direct C–H borylation under transition metal-free conditions have been reported,[9] although the material were limited to either electron rich arenes or heterocycles, and air and moisture sensitive reagents were needed. Consequently, a practical, metal-free method that is rapid and effective, works under mild conditions with various readily available borylating reagents, shows high functional group suffer and avoids strong acids, bases and harful reagents is still highly desirable. Herein, we wish to report our discovery and development of a new borylation reaction of aryl halides using bright as a proper reagent (Scheme 1e).10

Results

previously, a solution of 4-iodoanisole (1a) and bis(pinacolato) diboron (2) in acetonitrile was placed in a quartz test tube and irradiated with a 300W high pressure mercury lamp(maximumat 365 nm) for 3 hours. To inspire, the desired aryl-B(pin) product 3a was formed in 29% yield based on ^{1}H NMR analysis of the raw product(Table1,entry1).Other polar solvents such as trifluoroethanol and methanol did not improve the reaction (entries 2 and 3). Adding water and acetone as co-solvents was beneficial in both cases and increased the yield to 46% (entries 4 and 5). Showing of various organic and inorganic additives revealed that an organic base, N,N,N^{0},N'-tetramethyldiamino-methane (TMDAM), could further improve the yield to 58% (entry 9). By comparison, other bases led to low grade results (entries 6–8). Interestingly, a greater amount of TMDAM led to a significantly lower yield (entry 10). Using two equivalents of B2(pin)2 could improve the yield to 74% (entry 11). Further optimization by changing the reaction concentration of 1a resulted in a higher yield (c¼0.1 M, 82% yield) (entry 12 vs. 11 and 13).

During the study, we observed gradual decomposition of B2(pin)2. We felt that continuous-ow photolytic conditions might help in reducing the amount of B2(pin)2by competitively accelerating the desired reaction. In comparison with a typical batch photoreactor, micro channel photochemical, reactors. have signicant benets for reaction efficiency, yield, reproducibility, material throughput and scale-up[11–13] Based on the method developed developed by Booker-Milburn11a and our own experience in ow chemistry,14 we designed and assembled a continuous-flow photochemical reactor. Thus, transparent uorinated ethylene propylene (FEP) tubing (reaction volume 780 mL) was coiled

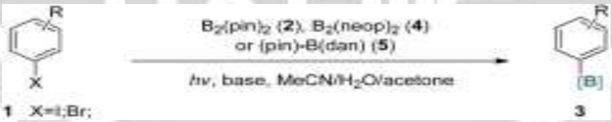
<table>
<tr><td colspan="5">Table 1. reaaction optmisation under batch and continuose- flow conditions</td></tr>
<tr><td colspan="5"> </td></tr>
<tr><td>Entry</td><td>(eq)</td><td>solvent</td><td>Additive (mol%)</td><td>Yield^{c}[%]</td></tr>
<tr><td colspan="5"><i>Batch condition</i>^{a}</td></tr>
<tr><td>1</td><td>1.0</td><td>MeCN</td><td>None</td><td>29</td></tr>
<tr><td>2</td><td>1.0</td><td>TFE</td><td>None</td><td>26</td></tr>
<tr><td>3</td><td>1.0</td><td>MeOH</td><td>None</td><td>15</td></tr>
<tr><td>4</td><td>1.0</td><td>MeCN/H2O</td><td>None</td><td>42</td></tr>
<tr><td>5</td><td>1.0</td><td>MeCN/H2O/acetone</td><td>None</td><td>46</td></tr>
</table>

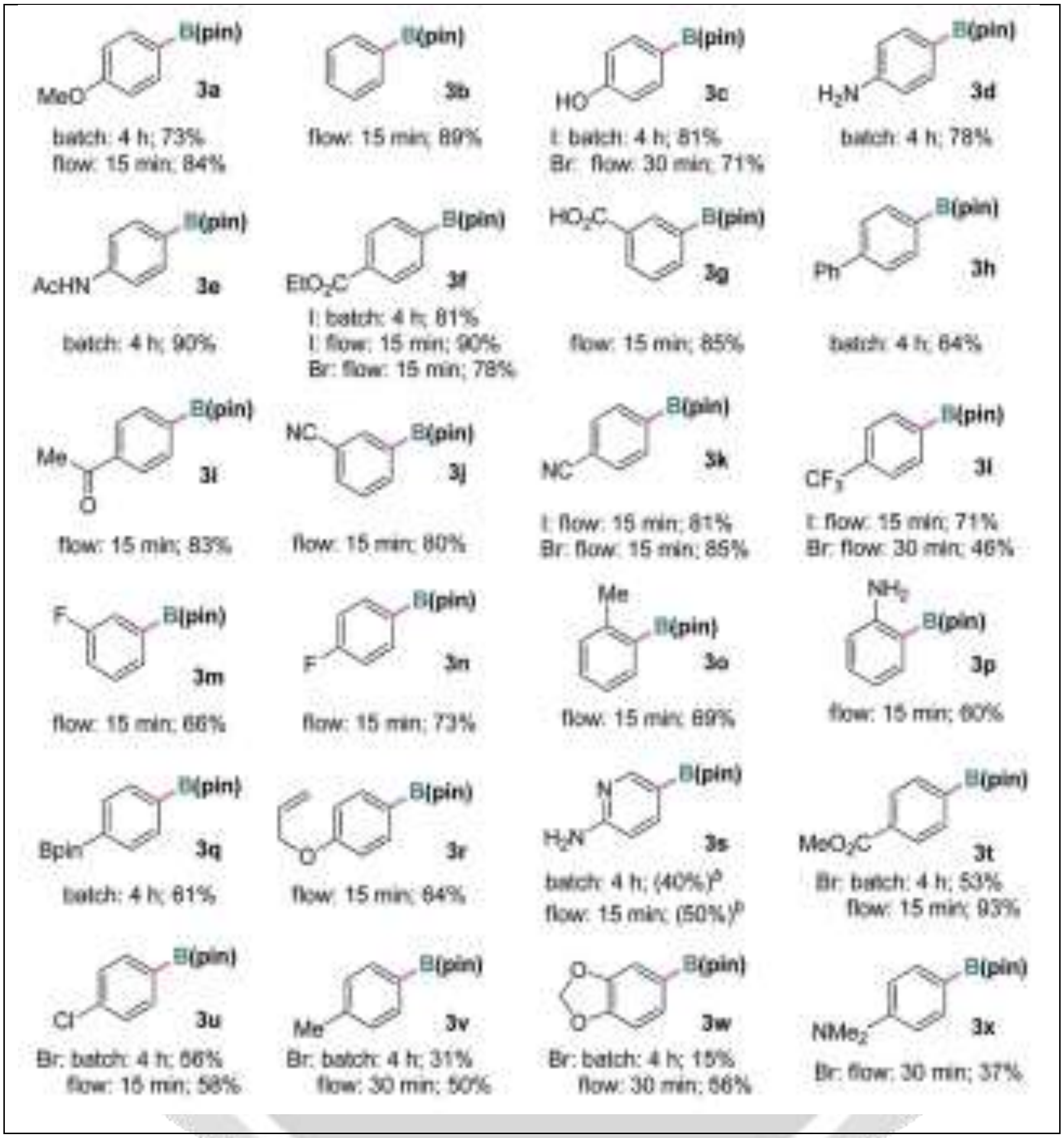
6	1.0	MeCN/H2O/acetone	Cs2CO3(100)	16
7	1.0	MeCN/H2O/acetone	KO^{t}Bu (100)	12
8	1.0	MeCN/H2O/acetone	TMEDA (50)	52
9	1.0	MeCN/H2O/acetone	TMDAM (50)	58
10	1.0	MeCN/H2O/acetone	TMDAM (50)	39
11	2.0	MeCN/H2O/acetone	TMDAM (100)	72
12[d]	2.0	MeCN/H2O/acetone	TMDAM (50)	81
13[e]	2.0	MeCN/H2O/acetone	TMDAM (50)	55
Batch condition[b]				
14	2.0	MeCN/H2O/acetone	TMDAM (50)	87
15	1.5	MeCN/H2O/acetone	TMDAM (50)	88

around a jacketed quartz immersion well in which the mercury lamp was situated. The reaction temperature was regulated by a cooling liquid circulating pump (see ESI†). A stock solution containing all reactants and reagents was introduced into the tubing using a syringe pump. To our delight, running the reaction under the same conditions as entry 12 but in continr uous-flow mode gave 3a in excellent yield (87%, entry 14) with a residence time of only 15 minutes. Indeed, the amount of B2(pin)2could be reduced to 1.5 equivalents without affecting the reaction efficiency (88% yield, entry 15).

With the optimized conditions in hand, we examined the substrate scope of the current borylation reaction under batch and/or continuous-flow conditions, as summarized in Table 2. Iodoarenes with various electron-donating, -neutral and -withI drawing groupsatthepara-,meta-,orortho-positions, including hydroxyl, amino, amide, ester, acid, ketone, cyano, fluorine, boronate and trifluoromethyl groups, were all efficiently conc verted to the corresponding aryl pinacol boronates in good to

Table 2. substrate scope of the photolytic borylation[a]





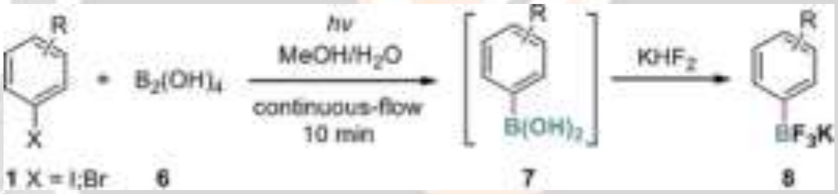
excellent yields (3a–3r). Groups potentially reactive under UV light such as aryl ketone (for 3i) and biaryl (for 3h) were compatible. Asubstrate containin ganally lether group was alsoviable (3r), which is interesting considering that the reaction might involve a reactive carbon-based radical and the double bond could be attacked. In addition, the borylation of 2-amino- 5-iodopyridine was possible, and a moderate yield of the cor5 responding boronate 3s was observed by^{1}H NMR spectroscopic analysis. Attempts to purify 3s were unsuccessful due to its decomposition on silica gel. Furthermore, when aryl bromides were subjected to the same reaction conditions, the desired products were produced in comparable or slightly lower yields than the iodides (3c, 3f, 3k, 3l and 3t–3x). Finally, different borylating reagents were utilized under otherwise identical conditions. Reactions using bis(neopentanediolato)diboron B2(neop)2 successfully afforded the desired products in good yields (3y and 3z). Interestingly,when an unsymmetrical diboron (pin)B–B(dan) was employed, selective introduction of theB(dan) moiety was realized (3aaand3ab)and no aryl pinacol.

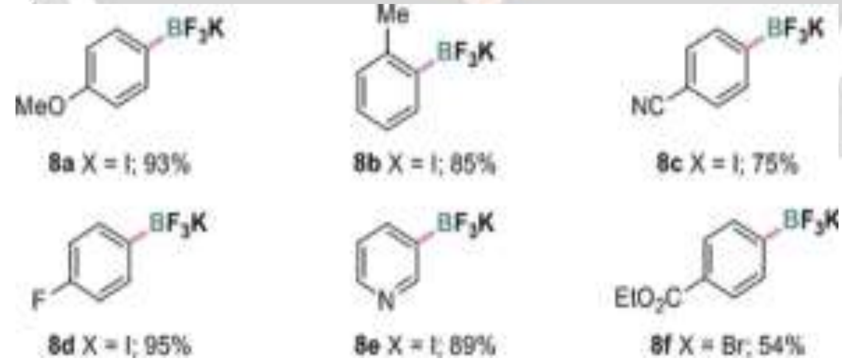
boronate was observed.15 To demonstrate the stability and usefulness of this reaction in larger scale preparation, the boru ylationreactionsofiodobenzene and4-iodophenolwerecarried out at gram scale (10.0 mmol) employing a commercial autoo mated flow chemistry system (reactor volume 7.8 mL, see ESI†). Without any further optimization, the reactions produced the desired arylboronate products in excellent isolated yields (3b 90% and 3c 93%) and the productivity corresponded to ~3 mmol h^{-1}.

Encouraged by the above results, we further investigated the possibility of using a more atom economical borylating reagent, bis-boronic acid (BBA, 6). Largely because its polar protic properties may not be amenable to most known borylation methods, this reagent has only recently been successfully used in palladium or nickel-catalyzed Miyaura borylation by Molander and coworkers.16 In the present borylation, pleasI ingly, we were able to convert 4-iodoanisole 1a to the corret sponding boronic acid 7a under continuous-flow conditions in quantitative yield based on ^{1}H NMR analysis (residence time 10 minutes). The key variation from the previous conditions was using aqueous methanol (MeOH: H_2O ¼ 4: 1 v/v) as the solvent. Due to the inconvenience of isolating the pure aryls boronic acid, aqueous KHF_2 was added and the resulting potassium aryltrifluoroborate 8a was obtained in 93% yield. Other aryl and heteroaryl iodides and a bromide were also transformed to the boronates in good to excellent yields in this manner (Table 3).

To gain insight into the reaction mechanism, and particuT larly to probe the role of additives and light, we conducted a series of control experiments (Table 4). When the batch reaction of 1f with $B_2(pin)_2$was run under the standard condiw tions, deiodination product 9 was formed in 7% yield in addition to the borylation product 3f (entry1).In the absence of Both TMDAM and light (entry 2), no conversion was observed. However, the reaction with 0.5 equivalents of TMDAM in the dark led to a small amount of 3f (entry 3); higher reaction temperatures and prolonged reaction time had little influence on the outcome.A hydrogen atom donor, Bu_3SnH,increased the conversion but led to 9 as the major product (entry 4). Furthermore,the reaction with Bu_3SnH under UV irradiation afforded 9 in high yield (entry 5). Similarly,using 9,10-dihyi droanthracene instead of Bu_3SnH, 9 (26%) and concomitant anthracene (11%)were observed (entry6).Finally, when TEMPO was added as a radical scavenger, the conversion was low and four products including 3f (15%), 9 (11%), the aryl-TEMPO adduct 10 (14%) and ethyl 4-hydroxybenzoate 11 (26%) were formed (entry 7).

Table 3. continuous-flow photolytic with $B_2(OH)_4$

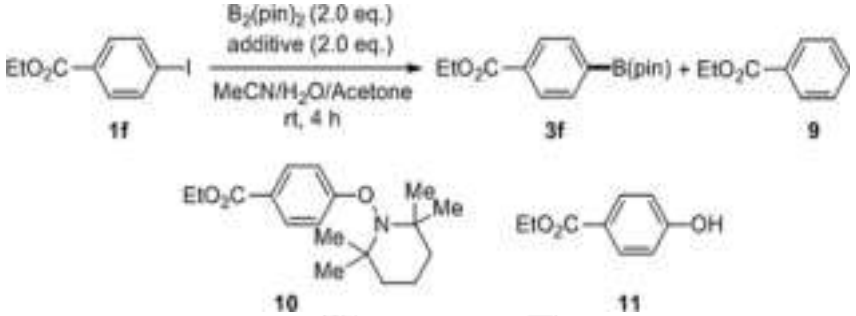




8a X = I; 93%
8b X = I; 85%
8c X = I; 75%
8d X = I; 95%
8e X = I; 89%
8f X = Br; 54%

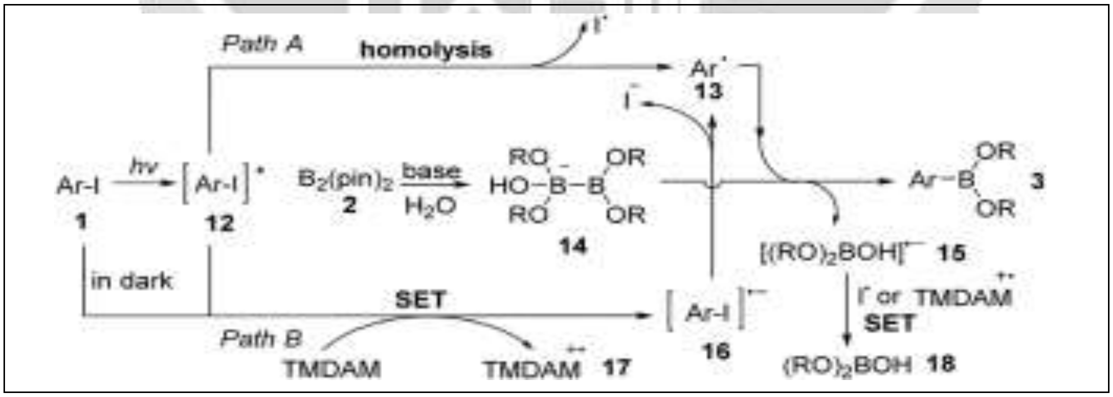
Based on the experimental results and related reports on photolytic reactions of aryl iodides,17 we propose two pathways both involving an aryl radical intermediate as the possible reaction mechanism (Scheme 2). The excited state 12 is generi ated by UV irradiation of aryl iodide 1. In path A, 12 undergoes homolytic C–I bond cleavage to form aryl radical 13 and

Table 4. Control experiments for preliminary mechanistic studies[a]



Entry	Light	TMDAM	Additive	Conversion [%]	Yield of 3f [%]	Yield of 9 [%]
1	+	+	-	100	81	7
2	-	-	-	0	0	0
3	-	+	-	13	13	0
4	-	+	Bu$_3$SnH	46	17	26
5	+	+	Bu$_3$SnH	100	18	80
6	+	+	DHA	68	42	26^b
7	+	+	TEMPO	69	15	11

Figure 2. proposed below mechanism reaction



Iodine aton. Ander aqueous conditions TMDAM activats a water molecule, combining with B2(pin)2(2) to form a sp^3–sp^2 diboron species 14.7,8f,18 Aryl radical 13 then reacts with 14 to produce arylboronate 3 and a boryl radical anion 15.19 15 can also be viewed as an anionic base-stabilized boryl radical.20 Alternatively, in path B, the excited state 12 or the starting aryl iodide 1 (when in darkness, although with low efficiency) is reduced by TMDAM via a single electron transfer (SET) process to form radical anion 16 and TMDAM-derived radical cation 17. 16 then undergoes C–I bond cleavage to generate aryl radical 13 and iodide anion. Finally, 15 is oxidized by the iodine atom frompathAor TMDAM-derived radical cation17 from path B to form borate 18 as a byproduct.

Conclusions

In summary we have discovered a novel and efficient photolytic borylation reaction of aryl halides using di boron reagents. this metal- free reaction features very mild condition, short reaction times generally high yields and broad functional group tolerance. Considering the reaction condition borylating reagent types and possible reaction mechanism, this work represents an important complementary approach the exiting C−B bond formation methods. Further studies on the mechanism and synthetic applications of this reaction are ongoing.

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