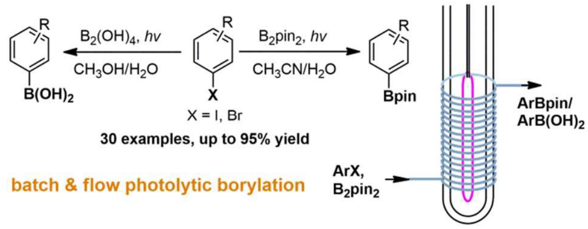
A metal-free C-B bond forming reaction from the corresponding aryl halides in batch and continuous-flow conditions is described.



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EDGE ARTICLE

Efficient Metal-Free Photochemical Borylation of Aryl Halides under Batch and Continuous-Flow Conditions

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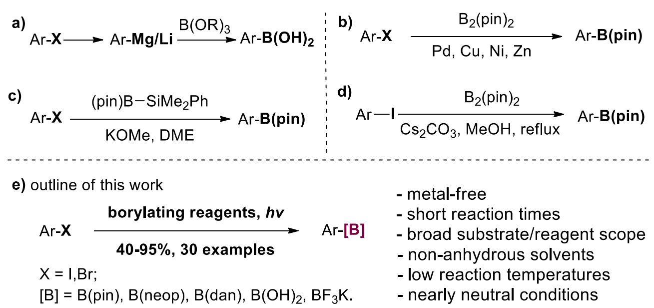
A rapid, chemoselective and metal-free C–B bond-forming reaction of aryl iodides and bromides in aqueous solution at low temperatures was discovered. This reaction is amenable to batch and continuous-flow conditions and shows exceptional functional group tolerance and broad substrate scope regarding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

Introduction

Arylboronic acids or esters have found broad applications in chemical, medicinal and materials sciences. In synthetic organic chemistry, in particular, they are versatile synthons for the formation of carbon-carbon or carbon-heteroatom bonds.[1] The conventional methods to generate arylboron compounds involved reactions of arylmetallic intermediates with trialkyl borates, followed by transesterification or hydrolysis. These reactions suffer some major drawbacks such as limited functional group tolerance as well as rigorous anhydrous conditions (Scheme 1a).[2] In the past decades, transition metal-catalyzed borylation reactions using palladium, nickel, copper and zinc have emerged as highly useful methods for conversion of a C-X bond to a C-B bond (Scheme 1b).[3] More recently, direct C-H borylation methods based on transition-metal catalysts have also been developed.[4] In order to reduce the costs and the heavy metal residues in the final products, several transition-metal-free methods toward 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 of Ce_2CO_3 as the promoter. The reaction time ranged from several hours to days and the yields were generally moderate (Scheme 1d).[6] Fernández and Muñiz transformed diaryliodonium acetates to arylboronates under mild conditions.[7] Using aryl amines as the starting material, Wang developed a mild and efficient Sandmeyer-type borylation process.[8a-c] Borylation of aryl diazonium salts[8d-f] and aryl triazenes[8g] were also reported. In addition, innovative methods for direct C-H borylation under transition metal-free conditions have been reported,[9] although the substrates 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 tolerance and avoids strong acids, bases and hazardous reagents, is still highly desirable. Herein, we wish to report our discovery and development of a new borylation reaction of aryl halides using light as a clean reagent (Scheme 1e).[10]



Scheme 1 Summary of borylation reactions of aryl halides and the outline of this work.

Results and discussion

Initially, a solution of 4-iodoanisole (**1a**) and bis(pinacolato)-diboron (**2**) in acetonitrile was placed in a quartz test tube and irradiated with a 300 W high pressure mercury lamp (maximum at 365 nm) for 4 hours. Encouragingly, the desired aryl-B(pin) product **3a** was formed in 29% yield based on ^{1}H NMR analysis

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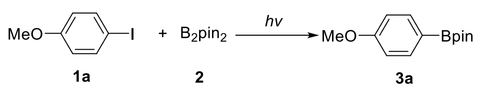
of the crude product (Table 1, entry 1). Other polar solvents such as methanol and trifluoroethanol did not improve the reaction (entries 2 and 3). Adding water and acetone as co-solvents were both beneficial and increased the yields to 46% (entries 4 and 5). Screening of various organic and inorganic additives revealed that an organic base, N,N,N',N'-tetramethyldiaminomethane (TMDAM), could further improve the outcome to 58% yield (entry 9). For comparison, other bases led to inferior results (entry 6-8). Interestingly, more amount of TMDAM led to significantly lower yield (entry 10). Using two equivalents of $B_2(pin)_2$ could improve the yield to 72% (entry 11). Further optimization by changing the reaction concentrations of **1a** resulted in higher yield (c = 0.1 M, 81% yield) (entry 12 vs. 11 and 13).

Table 1 Reaction optimization under batch and continuous-flow conditions

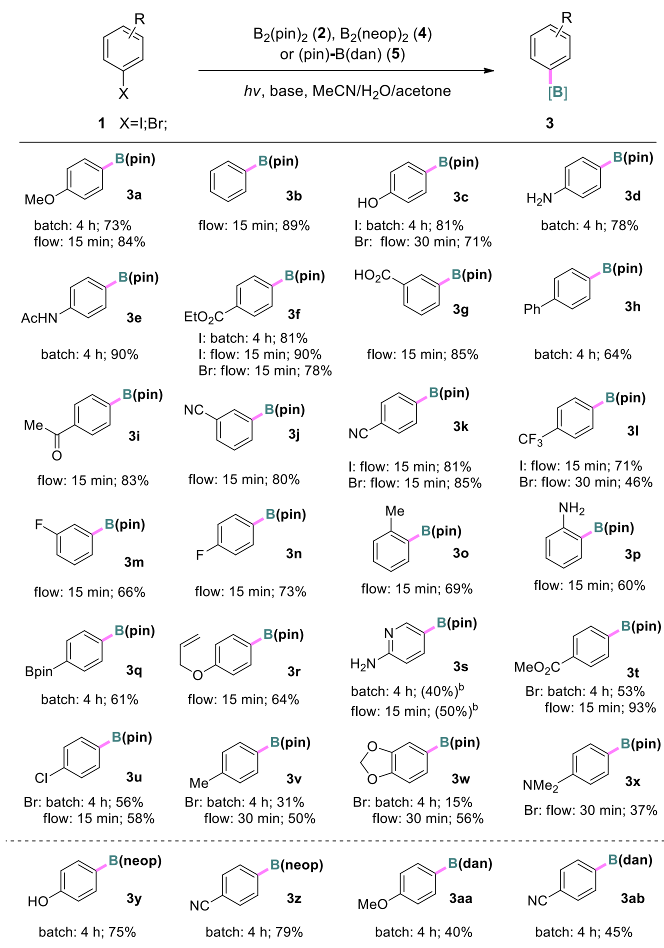


Entry	**2** (eq.)	Solvent	Additive (mol %)	Yield [%][c]
		Batch conditions[a]		
1	1.0	MeCN	none	29
2	1.0	TFE	none	26
3	1.0	MeOH	none	15
4	1.0	$MeCN/H_2O$	none	42
5	1.0	$MeCN/H_2O$/ Acetone	none	46
6	1.0	$MeCN/H_2O$/ Acetone	Cs_2CO_3 (100)	16
7	1.0	$MeCN/H_2O$/ Acetone	KO^tBu (100)	12
8	1.0	$MeCN/H_2O$/ Acetone	TMEDA (50)	52
9	1.0	$MeCN/H_2O$/ Acetone	TMDAM (50)	58
10	1.0	$MeCN/H_2O$/ Acetone	TMDAM (100)	39
11	2.0	$MeCN/H_2O$/ Acetone	TMDAM (50)	72
12[d]	**2.0**	**$MeCN/H_2O$/ Acetone**	**TMDAM (50)**	**81**
13[e]	2.0	$MeCN/H_2O$/ Acetone	TMDAM (50)	55
		Flow conditions[b]		
14	2.0	$MeCN/H_2O$/ Acetone	TMDAM (50)	87
15	**1.5**	**$MeCN/H_2O$/ Acetone -**	**TMDAM (50)**	**88**

[a] batch conditions: **1a** (0.1-0.2 mmol, c = 0.05 M/0.1 M), **2** (0.1-0.4 mmol), RT, 4 h; [b] flow conditions: **1a** (c = 0.1 M), -5 °C, residence time 15 min; [c] determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard; [d] c = 0.1 M; [e] c = 0.2 M; TMEDA: N,N,N,N-tetramethylethylenediamine; TMDAM: N,N,N',N'-tetramethyldiaminomethane.

During the study, we observed gradual decomposition of $B_2(pin)_2$. We felt that continuous-flow photolytic conditions might help in reducing the amount of $B_2(pin)_2$ by competitively accelerating the desired reaction. In comparison with a typical batch photoreactor, microchannel photochemical reactors have significant benefits on reaction efficiency, yield, reproducibility, material throughput and scaling-up.[11-13] Based on the method developed by Booker-Milburn[11a] and our own experience in flow chemistry,[14] we designed and assembled a continuous-flow photochemical reactor. Thus, transparent fluorinated ethylene propylene (FEP) tubing (reaction volume 780 μL) was coiled 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 SI). A stock solution containing all reactants and reagents was introduced into the tubing using a syringe pump. To our delight, running the reaction under conditions same as entry 12 but using a continuous-flow mode gave **3a** in excellent yield (87%, entry 15) with a residence time of only 15 minutes. Indeed, the amount of $B_2(pin)_2$ could be reduced to 1.5 equivalent without affecting the reaction efficiency (88% yield, entry 16).

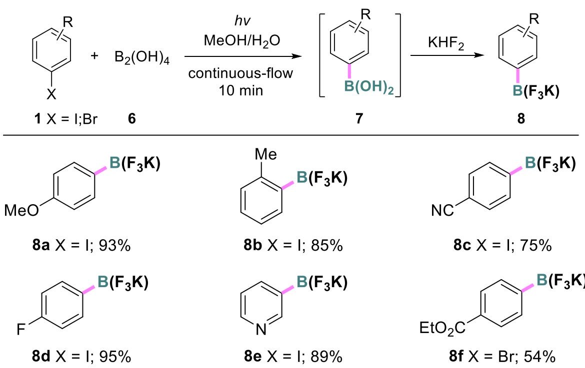
Table 2 Substrate scope of the photolytic borylation.[a]



[a] Batch conditions: **1a** (0.2 mmol, c = 0.1 M), **2** (0.4 mmol, 2.0 eq.), TMDAM (0.5 eq.), RT, 4 h; Flow conditions: **1a** (c = 0.1 M), **2** (1.5 eq.), TMDAM (0.5 eq.), -5 °C, residence time 15-30 min; [b] determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard; TMDAM: N,N,N',N'-tetramethyldiaminomethane.

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 -withdrawing groups at the *para*-, *meta*-, or *ortho*-positions, including hydroxyl, amino, amide, ester, acid, ketone, cyano, fluorine, boronate and trifluoromethyl groups, were all efficiently converted to the corresponding aryl pinacol boronates in good to excellent yields (**3a-3r**). Potentially reactive groups under UV light such as aryl ketone (for **3i**) and biaryl (for **3h**) were compatible. Interestingly, a substrate containing allyl ether group was also viable (**3r**), considering the reaction might involve reactive carbon-based radical and the double bond might be attacked. In addition, the borylation of 2-amino-5-iodopyridine was also possible and moderate yield of the corresponding boronate **3s** was observed by ^{1}H NMR spectroscopic analysis. Attempts to purify **3s** were not successful due to its decomposition on silica gel. Furthermore, when aryl bromides were subjected to the same reaction conditions, the desired products could be produced in comparable or slightly lower yields in comparison with the iodides (**3c**, **3f**, **3k**, **3l** and **3t**-**3x**). Finally, different borylating reagents were utilized under the otherwise identical conditions. Thus, the reactions using bis(neopentanediolato)diboron $B_2(neop)_2$ 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 the B(dan) moiety was realized (**3aa** and **3ab**) and no aryl pinacol boronate was observed.[15] To demonstrate the stability and usefulness of this reaction in larger scale preparation, the borylation of iodobenzene and 4-iodophenol were carried out in grams scale (10.0 mmol) employing a commercial automated flow chemistry system (with a reactor volume of 7.8 mL, see SI). 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}.

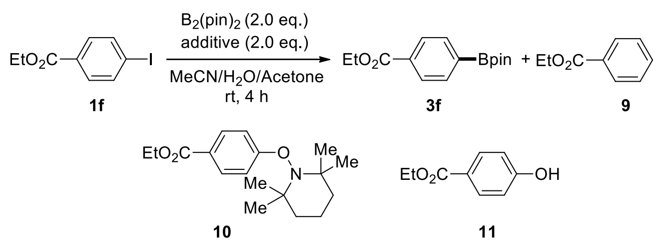
Table 3 Continuous-flow photolytic borylation with $B_2(OH)_4$



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 property 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, pleasingly, we were able to convert 4-iodoanisole **1a** to the corresponding 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 = 4:1 v/v) as the solvent. Due to the inconvenience to isolate the pure arylboronic 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 insights into the reaction mechanism, particularly to probe the roles 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 conditions, 7% of deiodination product **9** was formed accompanying the borylation product **3f** (entry 1). In the absence of both TMDAM and light (entry 2), no conversion was observed. However, the reaction with 0.5 equivalent of TMDAM in dark led to 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 afforded **9** in high yield under UV irradiation (entry 5). Similarly using 9,10-dihydro-anthracene instead of Bu_3SnH, **9** (26%) and concomittant anthracene (11%) were observed (entry 6). 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 4 Control experiments for preliminary mechanistic study[a]

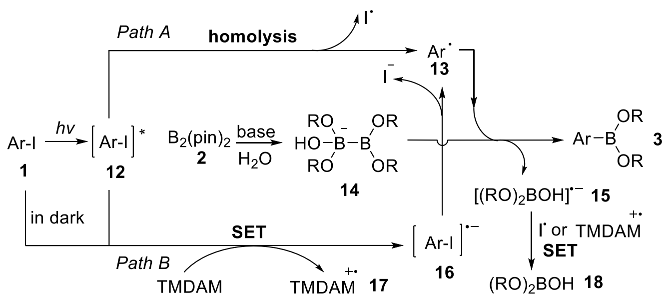


Entry	Light	TMDAM	Additive	Conversion [%]	Yield of **3f** [%]	Yield of **9** [%]
1	+	+	-	100	81	7
2	-	-	-	0	0	0
3	-	+	-	13	13	0
4	-	+	Bu_3SnH	46	17	26
5	+	+	Bu_3SnH	100	18	80
6	+	+	DHA	68	42	26[b]
7	+	+	TEMPO	69	15	11

[a] Reactions were run in batch and yields were determined by ^{1}H NMR spectroscopic analysis with 1,3,5-trimethoxybenzene as an internal standard; [b] 11% of anthracene was formed. TMDAM: N,N,N',N'-tetramethyldiaminomethane; DHA: 9,10-dihydroanthracene; TEMPO: (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

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). Thus, the excited state **12** may be generated by UV irradiation of aryl iodide **1**. In path A, **12** can undergo homolytic C-I bond cleavage to form aryl radical **13** and an iodine atom. Under aqueous conditions, TMDAM might activate water molecule, with $B_2(pin)_2$ (**2**), to form a sp^3-sp^2 diboron species

14.[18,7a,7b,8f] Aryl radical **13** then might react 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 dark although in low efficiency) might be reduced by TMDAM via a single electron transfer (SET) process to form radical anion **16** and TMDAM-derived radical cation **17**. **16** should then undergo C-I bond cleavage to generate aryl radical **13** and iodine anion. Finally, **15** could be oxidized by the iodine atom from path A or TMDAM-derived radical cation **17** from path B to form borate **18** as a byproduct.



Scheme 2 Proposed reaction mechanism

Conclusions

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

Acknowledgements

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