Direct bromodeboronation of arylboronic acids with CuBr$_2$ in water

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ABSTRACT

An efficient and practical method has been developed for the preparation of aryl bromides *via* the direct bromodeboronation of arylboronic acids with CuBr$_2$ in water. This strategy provides several advantages, such as being ligand-free, base-free, high yielding, and functional group tolerant.

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Aryl halides are valuable synthetic intermediates in organic chemistry that have been widely applied in carbon–carbon and carbon-heteroatom bond formation [1]. Especially, aryl bromides can be utilized in various coupling reactions to obtain functionalized cores [2]. Therefore, the exploration of efficient, regioselective and concise methods for the preparation of aryl bromides is of great importance. Traditional methods for the synthesis of aryl bromides such as the Sandmeyer reaction [3] and direct electrophilic aromatic substitution with Br$_2$ [4] or NBS [5] often suffer from limitations including harsh reaction conditions, toxic reagents and solvents, and low yields. In addition, although transition metal-catalyzed C—H bromination of arenes represents an efficient choice, expensive palladium salts and phosphine ligands restricts the application [6].

Arylboronic acids are important organic chemical intermediates, which can be converted into aryl halides. In 2004, Szumigala and co-workers reported the synthesis of aryl bromides from arylboronic acids with 1,3-dihalo-5,5-dimethylhydantoin *via* NaOMe-catalyzed bromodeboronation (Scheme 1a) [7]. In 2011, Zhang and co-workers developed a copper-catalyzed halogenation reaction between arylboronic acids and halogen salts under oxygen (Scheme 1b) [8]. In 2017, He and co-workers developed the copper(I)-catalyzed bromodeboronation of arylboronic acids with *N*-bromosuccinimide (NBS) using a MCM-41-immobilized CuCl complex as the catalyst (Scheme 1c) [9]. In 2019, Fu and co-workers reported the use of poly (4-vinyl pyridine) supported bromine

complexes for the bromination of arylboronic acids in the presence of NaNO$_2$ (Scheme 1d) [10].

Although various bromodeboronation reactions of arylboronic acids has been reported, there are often limitations in these methods: (1) specific reagents need to be prepared, (2) ligands or bases are required, (3) requirement for special reaction condition, such as an oxygen atmosphere, and (4) toxic reagents and solvents. Therefore, it is still worthwhile to develop inexpensive and effective reaction conditions for the formation of aryl bromides from arylboronic acids.

Copper is an abundant and inexpensive metal, which is widely used in transition metal-catalyzed coupling reactions, such as Sonogashira cross-coupling, Ullmann coupling and Chan-Lam coupling [11]. In the reported studies, copper complexes have shown good catalytic activity toward the preparation of biaryls [12] and phenols [13] from arylboronic acids. Based on this, we envisioned that CuX$_2$ could promote the halogenation of arylboronic acids. To the best of our knowledge, there are no reports on the direct bromodeboronation of arylboronic acids with CuBr$_2$ to aryl bromides in water. In the present work, we have developed an efficient bromodeboronation of arylboronic acids for the synthesis of aryl bromides in water under ligand-free and base-free conditions.
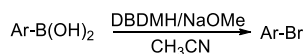
2-Methoxyphenylboronic acid (**1a**) was selected as a model substrate to identify the optimal reaction conditions (Table 1). Firstly, when 0.2 eq. CuBr$_2$ was used, 2-methoxyphenylboronic acid was not converted into the desired product in three different solvents (Table 1, Entries 1–3). When 10 mol% tetrabutylammonium bromide (TBAB) was added [14], aryl bromide **2a** was obtained in 12% yield in H$_2$O, and anisole **3a** was obtained in 26–33% yield *via* protodeboronation (Table 1, Entries 4–6). These

(a) Szumigala and co-workers, Ref. 7
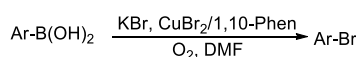
$$Ar\text{-}B(OH)_2 \xrightarrow[\text{CH}_3\text{CN}]{\text{DBDMH/NaOMe}} Ar\text{-}Br$$

(b) Zhang and co-workers, Ref. 8

$$Ar\text{-}B(OH)_2 \xrightarrow[\text{O}_2, \text{DMF}]{\text{KBr, CuBr}_2/1,10\text{-Phen}} Ar\text{-}Br$$

(c) He and co-workers, Ref. 9

$$Ar\text{-}B(OH)_2 \xrightarrow[\text{CH}_3\text{CN}]{\text{NBS, MCM-41-L-proline-CuBr}} Ar\text{-}Br$$

(d) Fu and co-workers, Ref. 10

$$Ar\text{-}B(OH)_2 \xrightarrow[\text{NaNO}_2, \text{CH}_3\text{CN}]{\text{PVP-Br}_2} Ar\text{-}Br$$

(e) *Present work*

$$Ar\text{-}B(OH)_2 \xrightarrow[\text{TBAB, H}_2\text{O}]{\text{CuBr}_2} Ar\text{-}Br$$
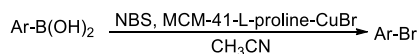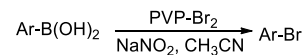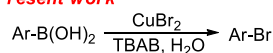
Scheme 1. Bromodeboronation of arylboronic acids.

Table 1
Optimization of the bromodeboronation of **1a**.[a],[b]
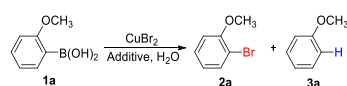
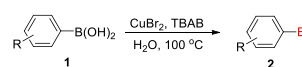| Entry	CuBr$_2$	Additive	Solvent	Yield (%)	
				2a	**3a**
1	0.2 eq.	–	H$_2$O	0	0
2	0.2 eq.	–	EtOH	0	0
3	0.2 eq.	–	CH$_3$CN	trace	trace
4	0.2 eq.	TBAB	H$_2$O	12	26
5	0.2 eq.	TBAB	EtOH	trace	33
6	0.2 eq.	TBAB	CH$_3$CN	trace	28
7	0.5 eq.	TBAB	H$_2$O	45	34
8	1.0 eq.	TBAB	H$_2$O	64	20
9	**1.5 eq.**	**TBAB**	**H$_2$O**	**82**	**trace**
10	2.0 eq.	TBAB	H$_2$O	70	10

[a] Reagents and conditions: arylboronic acid (1 mmol), additive (0.1 mmol), solvent (5 mL), sealed tube, 100 °C, 8 h.
[b] Isolated yield.

Table 2
Substrates scope for the bromodeboronation of arylboronic acids.[a],[b]

Entry	1	2	Yield (%)
1	**1a**	**2a**	82
2	**1b**	**2b**	85
3	**1c**	**2c**	80
4	**1d**	**2d**	78
5	**1e**	**2e**	88
6	**1f**	**2f**	92
7	**1g**	**2g**	88
8	**1h**	**2h**	90
9	**1i**	**2i**	81
10	**1j**	**2j**	85
11	**1k**	**2k**	80
12	**1l**	**2l**	84
13	**1m**	**2m**	81
14	**1n**	**2n**	87
15	**1o**	**2o**	82
16	**1p**	**2p**	87
17	**1q**	**2q**	90
18	**1r**	**2r**	72
19	**1s**	**2s**	89
20	**1t**	**2t**	90
21	**1u**	**2u**	73
22	**1v**	**1v**	90

[a] Reagents and conditions: arylboronic acid (1 mmol), CuBr$_2$ (1.5 mmol), TBAB (0.1 mmol), water (5 mL), sealed tube, 100 °C, 5–12 h.
[b] Isolated yield.

results indicated that H$_2$O was a better solvent than EtOH or CH$_3$CN. Upon increasing the amount of CuBr$_2$ from 0.2 eq. to 1.5 eq., the yield of bromodeboronated product **2a** increased from 45% to 82%, and the amount of deboronated product **3a** decreased. Notably, **2a** was obtained in 82% yield in the presence of 1.5 eq. CuBr$_2$ (Table 1, Entries 7–9). However, upon further increasing the amount to 2.0 eq. CuBr$_2$, the yield of **2a** decreased to 70% and by-product **3a** increased to 14% yield (Table 1, Entry 10). Therefore, the optimal conditions for the bromodeboronation of arylboronic acids was 1.5 eq. CuBr$_2$ in water at 100 °C in the presence of 10 mmol% TBAB.

With the optimal reaction conditions in hand, a series of arylboronic acids were investigated to study the scope of the direct bromodeboronation. To our delight, the bromodeboronation reactions of various arylboronic acids gave the corresponding aryl bromides in good to high yields (72–92%) in water (Table 2). Firstly, various arylboronic acids bearing electron-donating or electron-withdrawing groups gave the corresponding aryl bromides in good to high yields. Secondly, substituents on the aryl ring had minimal influence on the reaction; electron-donating groups (CH$_3$O, F, Cl, Br) gave similar yields as electron-withdrawing groups (NO$_2$, CN, CF$_3$). For example, 4-methoxyphenylboronic acid (**1b**) and 4-methyl phenylboronic acid (**1e**) gave **2b** and **2e** in 85% and 88%

yield, respectively. 3,5-Ditrifluoromethylphenylboronic acid (**1j**) and 4-cyanophenylboronic acid (**1l**) gave **2j** and **2l** in 84–85% yield. Finally, the steric hindrance of substituents on the arylboronic acids had no obvious influence. Various *ortho*-, *meta*- and *para*-substituted phenylboronic acids were examined, and the yields of the aryl bromides did not change with the increase of steric hindrance. Furthermore, we expanded the substrate scope to heterocyclic boronic acids (**1r-1v**) which gave the corresponding products in good yields (72–91%). Especially, **1t** and **1v** were both converted to **2t** and **2v** in 90% yield.

In addition, we carried out the gram-scale reaction of 4-morpholinophenylboronic acid **1h** (Scheme 2). The reaction proceeded
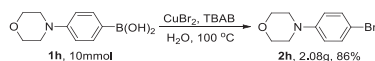
Scheme 2. Gram-scale synthesis of **2h**.

smoothly to afford the desired product **2h** in 86% yield; this indicated that the present strategy is practical for the large-scale preparation of aryl bromides.

In conclusion, we have developed a practical and efficient method for the preparation of aryl bromides *via* the direct bromodeboronation of arylboronic acids using $CuBr_2$ under mild conditions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152738.

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