Practical Transition-Metal-Free Protodeboronation of Arylboronic Acids in Aqueous Sodium Hypochlorite

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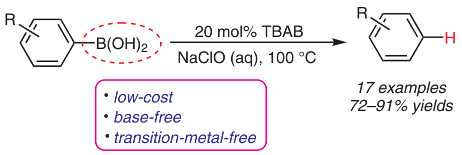

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Abstract A concise and practical method was developed for the protodeboronation of arylboronic acids under mild conditions in aqueous NaClO at 100 °C. The strategy is low-cost, transition-metal-free, and base-free.

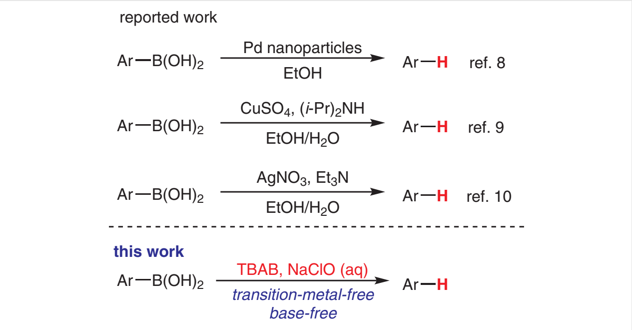
Key words protodeboronation, arylboronic acids, sodium hypochlorite

Arylboronic acids and their derivatives are valuable reagents that have been extensively used in cross-coupling reactions to construct C–C, C–O, C–N and C–X bonds.[1] In recent decades many reports have appeared on transition-metal-catalyzed Suzuki–Miyaura cross-coupling reactions of arylboronic acids to form biaryls.[2] In these reactions, protodeboronation of the arylboronic acid is a common side reaction, and was considered to be of no use in organic synthesis; consequently, it attracted little attention. In recent years, however, the deliberate removal of the $–B(OH)_2$ group has attracted increasing attention, and remarkable progress has been made. For example, Aggarwal and coworkers reported enantioselective syntheses of natural or nonnatural compounds through protodeboronation of allyl- and/or alkylboronic esters,[3,4] which markedly promoted the application of protodeboronation.

Transition-metal-catalyzed transformation reactions are widely used in organic synthesis,[5] and there have been several studies on transition-metal-catalyzed protodeboronations of arylboronic acids. As early as in 1930, Ainley and Challenger reported a protodeboronation with metallic salts, including $CuSO_4$, $CrBr_3$, and $ZnCl_2$, in organic solvents at high temperatures.[6] Subsequently, Klingensmith et al. found that phenylboronic acids bearing electron-donating substituents showed increased rates of protodeboronation in concentrated acid.[7] S.-T. Liu and co-workers reported that palladium nanoparticles efficiently catalyzed the deboronation of arylboronic acids in an alcoholic medium under basic conditions.[8] C. Liu et al. developed an efficient protocol for the copper- and silver-catalyzed protodeboronation of arylboronic acids in ethanolic media.[9,10] Although many reported methods are available for the protodeboronation of arylboronic acids through transition metal-catalyzed or other means, most require harsh conditions, such as the use of metallic salts as catalytic systems, bases, concentrated acids, and high temperatures, or use environmentally damaging solvents.[6–11] There is therefore still a need to develop efficient and green conditions for protodeboronation of arylboronic acids.

In previous work, when we performed Pd-catalyzed oxidative homocouplings of arylboronic acids in aqueous NaClO, we found that a few protodeboronated byproducts were formed under these conditions.[12] This indicated that arylboronic acids can undergo protodeboronation in aqueous NaClO, and that a metal catalytic system might be dispensable in this reaction. To the best of our knowledge, few reports have appeared on transition-metal-free conditions for this reaction.[13] We therefore explored and developed an efficient, transition-metal-free and base-free method for the protodeboronation of arylboronic acids in aqueous NaClO under mild conditions (Scheme 1).

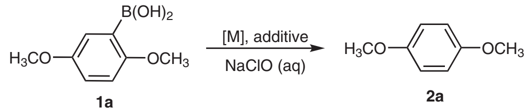
We chose (2,5-dimethoxyphenyl)boronic acid (**1a**) as a model substrate to identify the optimal reaction conditions, and we examined the effects of various transition-metal catalysts (Cu sources) and of TBAB as an additive (Table 1). To study the effect of various Cu sources on the protodeboronation of arylboronic acids, we performed the reaction in 10.5 wt% aqueous NaClO in the presence of various Cu salts [$CuSO_4$, $CuBr_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$]. Boronic acid **1a** was converted into 1,4-dimethoxybenzene (**2a**) in yields of 55, 51, and 56% in the presence of $CuSO_4$, $Cu(OAc)_2$, or $Cu(OTf)_2$,



Scheme 1 Protodeboronations of arylboronic acids

respectively (Table 1, entries 1, 3, and 7); however, when $CuBr_2$ was used, only a trace of **2a** was found (entry 5). When TBAB (20 mol%) was added, the yields of **2a** were significantly improved (entries 2, 4, 6, and 8); in particular, a yield of 87% was obtained in the presence of $CuSO_4$ and TBAB (entry 2). Next, we examined whether a transition-metal catalyst was necessary. In the absence of both a transition-metal catalyst and TBAB, the reaction in aqueous NaClO gave none of the required product (entry 9). Surprisingly however, when TBAB alone was added, the yield of **2a** increased to 88% (entry 10), which was higher than that obtained under any of the other conditions. Therefore, it was quite clear that the optimal conditions for protodeboronation of arylboronic acids involve the use of TBAB (20 mol%) in 10.5 wt% aqueous NaClO at 100 °C for 12 hours.

Table 1 Optimization of the Protodeboronation of (2,5-Dimethoxyphenyl)boronic acid (**1a**)[a]



1a **2a**

Entry	[M]	Additive	Yield[b] (%)
1	$CuSO_4$	–	55
2	$CuSO_4$	TBAB	87
3	$Cu(OAc)_2$	–	51
4	$Cu(OAc)_2$	TBAB	82
5	$CuBr_2$	–	trace
6	$CuBr_2$	TBAB	38
7	$Cu(OTf)_2$	–	56
8	$Cu(OTf)_2$	TBAB	79
9	–	–	0
10	–	**TBAB**	**88**

[a] Reaction conditions: **1a** (1 mmol), [M] (0.1 mmol), additive (0.2 mmol), 10.5 wt% aq NaClO (5 mL), 100 °C, 12 h.
[b] Isolated yield.

With the optimal reaction conditions in hand, a series of arylboronic acids were chosen to study the scope of the protodeboronation. In addition, to study the effects of the type of substituent group (electron-donating and electron-withdrawing groups) and the position of substituents (*ortho* or *para*), the reactions of various arylboronic acids were examined under the standard reaction conditions. To our delight, all substituted arylboronic acids gave the corresponding products in good yields in aqueous NaClO (Table 2). From these results, we inferred that the type of substituent group has little influence on the protodeboronation. For example, 2,5-(dimethoxyphenyl)boronic acid (**1a**) and (2-chlorophenyl)boronic acid (**1f**) were converted into the corresponding products **2a** and **2d** in yields of 88 and 82%, respectively; (4-morpholin-4-ylphenyl)boronic acid (**1h**) afforded product **2e** in 89% yield; and (2-nitrophenyl)boronic acid (**1k**) and [2-(trifluoromethyl)phenyl]boronic acid (**1l**) gave the corresponding products **2g** and **2h** in yields of 85 and 83%, respectively.

Table 2 Protodeboronation of Various Arylboronic Acids[a]

$$\underset{\mathbf{1}}{\text{Ar—B(OH)}_2} \xrightarrow[\text{NaClO (aq)}]{\text{TBAB}} \underset{\mathbf{2}}{\text{Ar—H}}$$

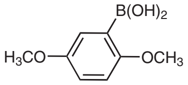
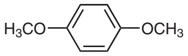
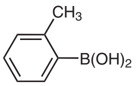
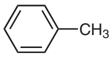
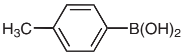
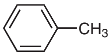
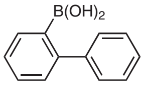
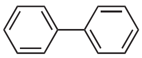
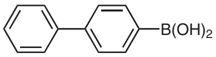
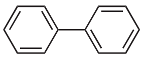
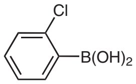
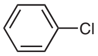
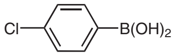
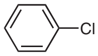
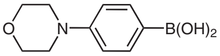
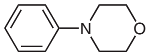
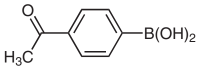
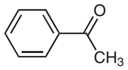
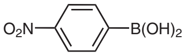
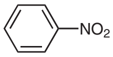
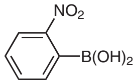
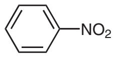
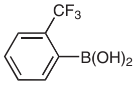
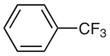
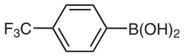
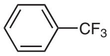
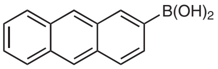
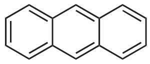
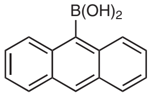
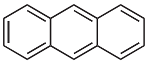
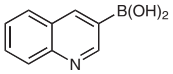
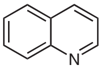
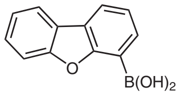
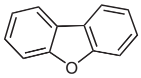
Entry	1	2	Yield[b] (%)
1	 **1a**	 **2a**	88
2	 **1b**	 **2b**	84[c]
3	 **1c**	 **2b**	72[c]
4	 **1d**	 **2c**	90
5	 **1e**	 **2c**	86
6	 **1f**	 **2d**	82[c]
7	 **1g**	 **2d**	74[c]
8	 **1h**	 **2e**	89

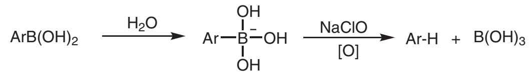
Table 2 (continued)

Entry	1	2	Yield[b] (%)
9	 **1i**	 **2f**	90
10	 **1j**	 **2g**	73
11	 **1k**	 **2g**	85
12	 **1l**	 **2h**	83
13	 **1m**	 **2h**	74
14	 **1n**	 **2i**	84
15	 **1o**	 **2i**	91
16	 **1p**	 **2j**	87
17	 **1q**	 **2k**	90

[a] Reaction conditions **1** (1 mmol), TBAB (0.2 mmol), 10.5 wt% aq NaClO (5 mL), 100 °C, 6–12 h.
[b] Isolated yield.
[c] Isolated without column chromatography.

Although arylboronic acids bearing electron-donating or electron-withdrawing groups were suitable for this reaction system, the position of the substituents had an obvious effect on protodeboronation. In general, greater steric hindrance of the arylboronic acid was beneficial to this reaction. In particular, the yields of *ortho*-substituted arylboronic acids (e.g., **1b**, **1d**, **1f**, **1k**, and **1l**) were higher than those of their *para*-substituted counterparts (e.g., **1c**, **1e**, **1g**, **1j**, **1m**) (Table 2, entries 2–13). Moreover, 2-anthrylboronic acid (**1n**) and 9-anthrylboronic acid (**1o**) gave anthracene (**2i**) in yields of 84 and 91%, respectively (entries 14 and 15). Finally, heterocyclic boronic acids were investigated to check their susceptibility to the reaction conditions. Pleasingly, quinolin-3-ylboronic acid (**1p**) and dibenzo[*b*,*d*]furan-4-ylboronic acid (**1q**) gave quinoline (**2j**) and dibenzo[*b*,*d*]furan (**2k**) in yields of 87 and 90%, respectively (entries 16 and 17). These results showed that our improved protocol for protodeboronation of arylboronic acids in water is both concise and broadly applicable.

Based on the results of our study, we propose the mechanism shown in Scheme 2 for the NaClO-promoted protodeboronation of arylboronic acids. Initially, the arylboronic acid undergoes addition of H_2O to form an intermediate arylboronate anion. This is oxidized by NaClO to give the required product, together with boric acid. In this process, TBAB acts as a promoter to accelerate the formation of the arylboronate anion, which leads to the oxidative protodeboronation.



Scheme 2 Proposed mechanism for protodeboronation of arylboronic acids

In conclusion, we have developed a concise and practical method for the protodeboronation of arylboronic acids under mild conditions in aqueous NaClO.[14] This strategy tolerates a broad scope of arylboronic acids and is low-cost, transition-metal-free, and base-free.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706298.

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(14) **Protodeboronation of Arylboronic Acids; General Procedure**
A solution of the appropriate arylboronic acid (1 mmol) and TBAB (64 mg, 0.2 mmol) in 10.5 wt% aq NaClO was stirred at 100 °C for 6–12 h until the reaction was complete (TLC). The mixture was extracted with Et_2O (2 × 5 mL), and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography [silica gel, PE–EtOAc (40:1 to 20:1)].

1,4-Dimethoxybenzene (**2a**)
Prepared from **1a** according to the general procedure as a white solid; yield: 121 mg (88%); mp 51–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (s, 4 H), 3.78 (s, 6 H).