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Base-promoted silver-catalyzed protodeboronation of arylboronic acids and esters†

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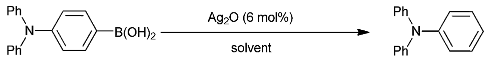
The silver-catalyzed protodeboronation of arylboronic acids and esters in the presence of a base was developed. This method was highly efficient for the protodeboronation of various arylboronic acids and was applied to an efficient deprotection of bifunctional amine under mild conditions. A base-promoted mechanism was proposed.

Organoboronic acids and their derivatives have been extensively used in organic synthesis, in particular, in the transition-metal-catalyzed Suzuki–Miyaura cross-coupling reaction, due to their unique reactivity, ready availability, and low toxicity.[1] The protodeboronation is a common, sometimes even dominant side reaction in the Suzuki–Miyaura cross-coupling reaction.[2] Over the past decades, the protodeboronation was considered to be useless in organic syntheses, thus, only a few studies were reported in the literature.[3] Until recent years, the protodeboronation has attracted increasing attention, and remarkable progress in the application of protodeboronation to organic syntheses has been achieved by several groups.[4] For example, Aggarwal's group[5] reported a series of investigations on highly enantioselective syntheses of natural and non-natural products using the protodeboronation of allylic and/or alkyl boronic esters, which greatly promoted the application of protodeboronation. However, the protodeboronation of arylboronic acids and esters has received little attention as a viable synthetic method from the synthetic community. In 2013, Cheon's group[6] reported metal-free thermal protodeboronation of *ortho*- and *para*-phenol boronic acids in wet DMSO. Very recently, the same group[7] has successfully extended the metal-free thermal protodeboronation to variable electron-rich arylboronic acids. In 2014, Perrin's group[8] developed an efficient protocol for the protodeboronation of electron-deficient 2,6-disubstituted arylboronic acids at pH 12. Although lots of efforts have been devoted to improve the efficiency of the protodeboronation, the reported protocols still suffer from a limited substrate scope. In a previous report, we have developed a copper-catalyzed protodeboronation of arylboronic acids under aqueous and aerobic conditons.[9] Herein, we report a general and efficient approach for the silver-catalyzed protodeboronation of a broad range of aryl boronic acids and esters in the presence of a base in aqueous media. Both electron-rich and electron-poor arylboronic acids could afford the products in excellent yields under the optimized conditions.

Initially, we investigated the influences of different reaction parameters on the protodeboronation reaction. The protodeboronation of 4-(diphenylamino)phenylboronic acid was chosen as a model reaction to screen the reaction conditions. In the presence of Ag_2O (6 mol%) and $K_3PO_4 \cdot 3H_2O$ (0.2 mmol),

Table 1 Effect of solvent on protodeboronation of 4-(diphenylamino)phenylboronic acid[a]



Entry	Solvent	Yield[b] (%)
1	$EtOH/H_2O$	98
2	DMF/H_2O	92
3	*i*-$PrOH/H_2O$	90
4	EtOH	91
5	DMF	22
6	Toluene	35
7	Ethylene glycol	70
8	PEG-400	45
9	H_2O	38

[a] Reaction conditions: 4-(diphenylamino)phenylboronic acid (0.2 mmol), Ag_2O (6 mol%), $K_3PO_4 \cdot 3H_2O$ (0.2 mmol), solvent (0.5 mL/0.5 mL), 80 °C, 30 min under air. The reaction was monitored by TLC. [b] Isolated yields.

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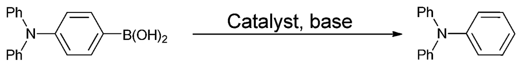
various solvents were tested at 80 °C. As shown in Table 1, excellent yields could be obtained in $EtOH/H_2O$, DMF/H_2O, *i*-$PrOH/H_2O$ and EtOH (Table 1, entries 1–4), and 50% aqueous ethanol was the best choice.

Next, we explored the effects of metal-catalysts on the same model reaction. All of the tested silver catalysts gave satisfactory results (Table 2, entries 1–5), and a 97% yield was obtained within shorter reaction time using $AgNO_3$ as catalyst (Table 2, entry 2). Subsequently, the effects of bases were investigated. As for the inorganic bases, $K_3PO_4 \cdot 3H_2O$ gave a satisfactory yield (97%), however, others including NaOH, CH_3ONa and K_2CO_3 were less effective than $K_3PO_4 \cdot 3H_2O$ (Table 2, entries 6–8). Compared to the inorganic bases, the organic bases demonstrated higher efficiency (Table 2, entries 9–12). The best base for this transformation is Et_3N, which provided a 96% yield in 10 min (Table 2, entry 12). In order to understand the function of the base in the present protocol, we investigated the effects of the loading of Et_3N in the same protodeboronation (Table 2, entries 12–15). Interestingly, the reaction still afforded the product in a high yield of 97% in 60 min by using 0.06 equiv. Et_3N which was the equal amount of silver catalyst (Table 2, entry 14). While further decreasing the amount of Et_3N to 0.03 equiv., the yield was decreased to 67% (Table 2, entry 15). It is worth noting that only a 16% yield of the product was obtained in the absence of a silver catalyst (Table 2, entry 16). The protodeboronation using 0.1 equiv. $K_3PO_4 \cdot 3H_2O$ or $K_3PO_4 \cdot 7H_2O$ as base was also carried out, providing 91% and 80% yields in 150 min, respectively (Table 2, entries 17 and 18). However, no products were observed in the absence of a base (Table 2, entry 19) or in the presence of CH_3COOH (Table 2, entry 20). The results show that the combination of a silver catalyst and a base plays a crucial role in the high efficiency on this reaction.

Table 2 Screening of optimum conditions for the protodeboronation of 4-(diphenylamino)phenylboronic acid[a]

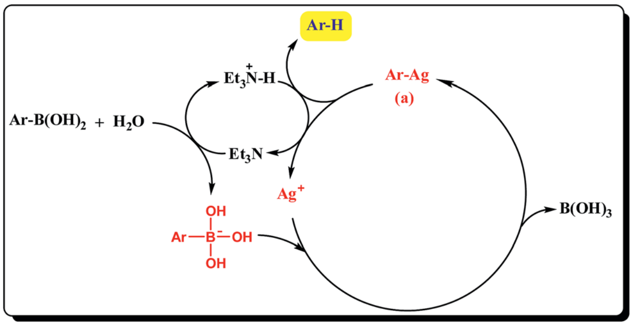


Entry	Catalyst	Base	Time (min)	Yield[b] (%)
1	Ag_2CO_3	$K_3PO_4 \cdot 3H_2O$	25	96
2	$AgNO_3$	$K_3PO_4 \cdot 3H_2O$	25	97
3	Ag_2O	$K_3PO_4 \cdot 3H_2O$	30	97
4	$AgBF_4$	$K_3PO_4 \cdot 3H_2O$	30	88
5	AgOAc	$K_3PO_4 \cdot 3H_2O$	30	94
6	$AgNO_3$	NaOH	30	59
7	$AgNO_3$	CH_3ONa	30	66
8	$AgNO_3$	K_2CO_3	30	57
9	$AgNO_3$	*i*-$PrNH_2$	30	95
10	$AgNO_3$	(*n*-Pr)$_3$N	13	97
11	$AgNO_3$	DBU	12	97
12	$AgNO_3$	Et_3N	10	96
13	$AgNO_3$	Et_3N (0.10 equiv.)	55	97
14	$AgNO_3$	Et_3N (0.06 equiv.)	60	97
15	$AgNO_3$	Et_3N (0.03 equiv.)	420	67
16	—	Et_3N (0.06 equiv.)	60	16
17	$AgNO_3$	$K_3PO_4 \cdot 3H_2O$ (0.10 equiv.)	150	91
18	$AgNO_3$	$K_3PO_4 \cdot 7H_2O$ (0.10 equiv.)	150	80
19	$AgNO_3$	—	60	0
20	$AgNO_3$	CH_3COOH	60	0

[a] Reaction conditions: 4-(diphenylamino)phenylboronic acid (0.2 mmol), catalyst (6 mol%), base (0.2 mmol), $EtOH/H_2O$ (0.5 mL/0.5 mL), 80 °C, under air. The reaction was monitored by TLC. [b] Isolated yields.

Based on the above results, a possible mechanism for the silver-catalyzed protodeboronation is depicted. As shown in Scheme 1, initially, arylboronic acid as a mild organic Lewis acid quickly transforms to a tetrahedral adduct arylboronate anion under alkaline conditions. Then, the silver ion attacks this tetrahedral adduct to provide an arylsilver intermediate (a). Subsequently, the arylsilver undertakes the protolysis with Et_3N^+H to deliver the arenes. The catalytic cycle is completed by generating the silver ion, which is accordance with the literature reports.[10] In this process, the base performs as a promoter to accelerate the formation of arylboronate anion, which leads to a fast silver-catalyzed protodeboronation of arylboronic acids.

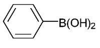
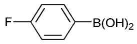
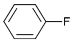
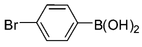
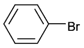
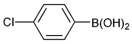
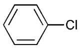
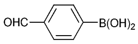
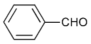
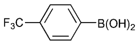
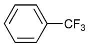
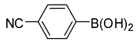
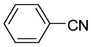
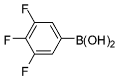
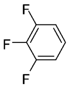
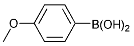
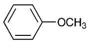
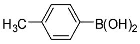
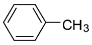
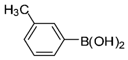
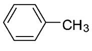
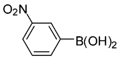
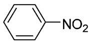
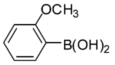
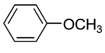
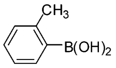
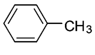
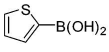
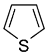
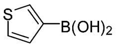
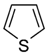
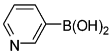
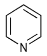
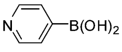
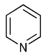
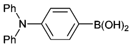
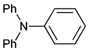
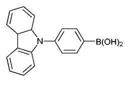
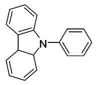
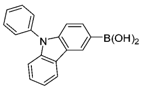
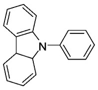
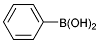
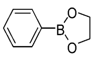
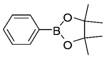
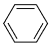
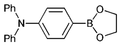
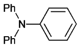
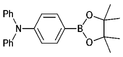
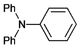
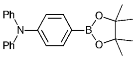
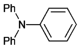
With the optimized conditions at hand, we further explored the scope and limitations of substrates for this protocol. As shown in Table 3, the electronic effects of the substituents on the arylboronic acids had little influence (Table 3, entries 1–10). Phenylboronic acid performed the protodeboronation smoothly and afforded a 95% yield of product (Table 3, entry 1). Both electron-poor (Table 3, entries 2–8) and electron-rich (Table 3, entries 9 and 10) arylboronic acids underwent the protodeboronation quickly and provided the products in excellent yields. For example, *p*-tolylboronic acid, which was ineffective in the metal-free thermal protodeboronation,[7] could afford the product in 92% yield in 10 min (Table 3, entry 10), and 4-(trifluoromethyl)phenylboronic acid was also very effective in this system compared to a previous method[8] (Table 3, entry 6). A large array of functional groups was tolerated in this system. The arylboronic acids with a $-CH_3$ or $-NO_2$ group at the *meta*-position also gave excellent yields in 20 min (Table 3, entries 11 and 12). The effects of steric hindrance were tested. The standard conditions were proved to be efficient to 2-



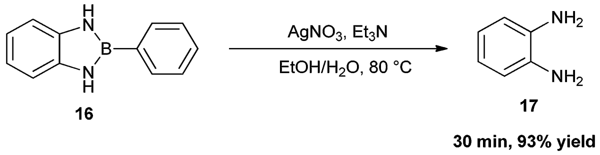
Scheme 1 A plausible mechanism of protodeboronation.

Table 3 Protodeboronation reaction of arylboronic acids and esters[a]

$$\text{Ar-BR} \xrightarrow[\text{EtOH/H}_2\text{O}]{\text{AgNO}_3\text{,Et}_3\text{N}} \text{Ar-H}$$

Entry	Ar-BR	Product		Time (min)	Yield[b] (%)
1			**1**	15	95
2			**2**	23	97
3			**3**	15	96
4			**4**	15	98
5			**5**	15	95
6			**6**	18	98
7			**7**	17	98
8			**8**	10	97
9			**9**	10	98
10			**10**	10	92
11			**10**	14	94
12			**11**	20	96
13			**9**	15	96
14			**10**	13	92
15			**12**	15	98
16			**12**	15	97
17			**13**	25	95
18			**13**	270	98
19			**14**	10	97[c]
20			**15**	15	98[c]
21			**15**	15	97[c]
22			**1**	15	95[d]
23			**1**	35	96
24			**1**	50	96
25			**14**	40	96[c]
26			**14**	55	92[c]
27			**14**	180	0[e]

[a] Reaction conditions: arylboronic acid and esters (0.2 mmol), $AgNO_3$ (6.0 mol%), Et_3N (0.2 mmol), $EtOH/H_2O$ (0.5 mL/0.5 mL), 80 °C, under air. The reaction was monitored by TLC. [b] GC yields. [c] Isolated yields. [d] Phenylboronic acid (2 mmol). [e] Anhydrous toluene as solvent, under N_2.



Scheme 2 Silver-catalyzed protodeboronation of a heterocyclic adduct.

methoxyphenylboronic acid and *o*-tolylboronic acid (Table 3, entries 13 and 14). It's worth noting that heterocyclic boronic acids exhibited high reactivity in this protocol (Table 3, entries 15–18). Various polycyclic aromatic boronic acids, which were rarely tested in literature, were highly effective in this system (Table 3, entries 19–21). For example, 4-(9*H*-carbozol-9-yl)phenylboronic acid afforded the product in 98% yield within 15 min (Table 3, entry 20). In addition, the protodeboronation could be scaled up to 2 mmol, and a 95% yield was readily achieved in the case of phenylboronic acid (Table 3, entry 22). To further explore the scope, the protodeboronation of organoboronic esters were tested. As expected, the cyclic esters of arylboronic acids gave satisfactory results (Table 3, entries 23–26). However, 4-(diphenylamino) phenylboronic acid pinacol ester did not undergo protodeboronation when anhydrous toluene was used as solvent under N_2 (Table 3, entry 27). This result could prove that the proton is transferred from the protic solvent, which is consistent with Cheon's report.[6]

There are only a few reports on the application of protodeboronation of arylboronic acids.[6,11] For example, phenylboronic acid reacts with *o*-phenylendiamine to give a stable heterocyclic adduct (Scheme 2, compound **16**) for the protection of free amino groups. However, the hydrolysis of adduct **16** required a relatively long period of eight hours.[11] Thus, we further studied the deprotection of the adduct **16** in the present silver-catalyzed protodeboronation system. As shown in Scheme 2, the protodeboronation performed effectively and a 93% yield of *o*-phenylendiamine **17** was obtained in 30 min.

Conclusions

In conclusion, we have developed a general, simple and highly efficient method for the silver-catalyzed protodeboronation of arylboronic acids and esters in aqueous media. The reactions proceeded smoothly in the presence of Et_3N under aerobic conditions. This method could be applied to a facile and efficient deprotection of bifunctional amines under mild conditions. The synthetic application of this approach is currently under investigation in our laboratory.

Experimental

Materials and methods

All arylboronic acids and esters, metal catalysts were used as received. Other reagents and solvents were obtained from commercial suppliers and used without further purification. All reagents were weighed and handled in air at room temperature. ^1H NMR spectra were recorded on a 400 MHz spectrometer using TMS as internal standard. The yields of liquid products were determined by GC using biphenyl as an internal standard, and the solid products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60–90 °C), unless otherwise noted. Compounds described in the literature were characterized by ^1H NMR spectra compared to reported data.

Typical procedure for protodeboronation of arylboronic acids and esters

A mixture of arylboronic acid or ester (0.2 mmol), $AgNO_3$ (6 mol%), Et_3N (0.2 mmol) and $EtOH/H_2O$ (0.5 mL/0.5 mL) was stirred at 80 °C in air for the indicated time. The mixture was added to brine (2 mL) and extracted three times with ethyl acetate (2 mL). The combined organic layers were dried over sodium sulfate and was analysed by gas chromatography using biphenyl as internal standard.

Typical procedure for protodeboronation of polycyclic aromatic boronic acids and esters

A mixture of arylboronic acid or esters (0.2 mmol), $AgNO_3$ (6 mol%), Et_3N (0.2 mmol) and $EtOH/H_2O$ (0.5 mL/0.5 mL) was stirred at 80 °C in air for the indicated time. The mixture was added to brine (10 mL) and extracted three times with ethyl acetate (10 mL). The solvent was concentrated under vacuum, and the product was isolated by short-column chromatography.

The procedure for protodeboronation of 2-phenyl-2,3-dihydro-1*H*-1,3,2-benzodiazaborole (16)

A mixture of 2-phenyl-2,3-dihydro-1*H*-1,3,2-benzodiazaborole (**16**) (0.2 mmol, 38.81 mg), $AgNO_3$ (6 mol%, 2.04 mg), Et_3N (0.2 mmol, 20.24 mg) and $EtOH/H_2O$ (0.5 mL/0.5 mL) was heated at 80 °C in Schlenk flask for 30 min. The mixture was added to brine (10 mL) and extracted three times with ethyl acetate (10 mL). The solvent was concentrated under vacuum, and the product was isolated by short-column chromatography using petroleum ether/ethyl acetate (1 : 1) and white solid was obtained (20.2 mg, 93% yield).

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