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Protodeboronation of ortho- and para-Phenol Boronic Acids and Application to ortho and meta Functionalization of Phenols Using Boronic Acids as Blocking and Directing Groups

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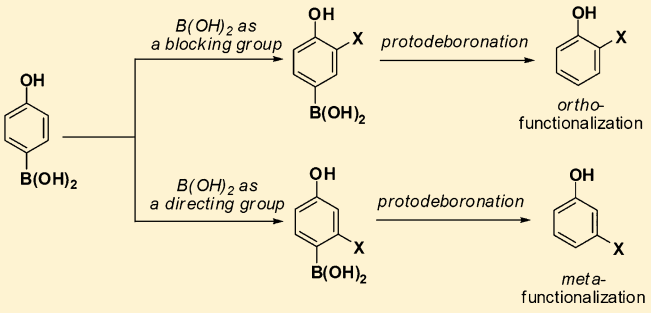
Supporting Information

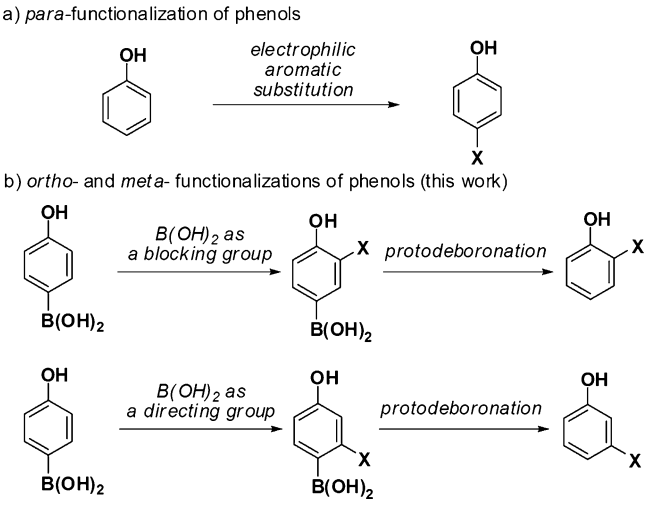
ABSTRACT: The first metal-free thermal protodeboronation of ortho- and para-phenol boronic acids in DMSO was developed. The protodeboronation was successfully applied to the synthesis of ortho- and meta-functionalized phenols using the boronic acid moiety as a blocking group and a directing group, respectively. Mechanistic studies suggested that this protodeboronation proceeds through the coordination of water to the boron atom followed by σ-bond metathesis.



INTRODUCTION

Phenol and its derivatives have been considered one of the most important commodity chemicals in modern chemical science and have been widely used as precursors to many materials and pharmaceutical drugs.[1] Thus, great efforts have been made to selectively functionalize phenols at specific positions relative to the phenolic hydroxyl group. One of the most common reactions used to introduce functional groups onto the phenol ring is the electrophilic aromatic substitution (EAS) reaction.[2] In general, EAS reactions of phenol derivatives afford para-functionalized phenols with ease (Scheme 1a), whereas until recently few methods to access functionalized phenol derivatives at other positions, particularly meta-functionalized phenols, had been developed.[3−5] Herein, we report a novel method to access ortho- and meta-functionalized phenol derivatives using a boronic acid as both a blocking group[6] and a directing group,[7,8] respectively, and the subsequent removal of the boronic acid moiety via protodeboronation (Scheme 1b). These results are based on our new findings of metal-free thermal protodeboronations of ortho- and para-phenol boronic acids in DMSO.

Scheme 1. Selective Functionalization of Phenols[a]



[a](a) Conventional approach for para functionalization. (b) New ortho and meta functionalization using a boronic acid as a blocking and directing group, respectively.

RESULTS AND DISCUSSION

Boronic acids and their derivatives are deemed an attractive class of synthetic intermediates because of their unique reactivity, ready availability, and low toxicity[9] and thus have been widely used in organic synthesis, in particular, in metal-catalyzed cross-coupling reactions.[10,11] Although there were a few reports of the protodeboronation of allylic and/or alkyl boronic esters as stereoselective synthetic methods,[12] the protodeboronation of aryl boronic acids, which is known as one of the most common side-reactions in metal-catalyzed coupling protocols,[13] has received little attention as a viable synthetic method from the synthetic community. This is not only because protodeboronation takes place under relatively harsh reaction conditions but also because the exact reaction mechanism and parameters to control such transformations are poorly understood.

Very recently, we developed a new step-economical method for the synthesis of both (*R*)- and (*S*)-BINOL derivatives through the diastereomeric resolution of racemic BINOL

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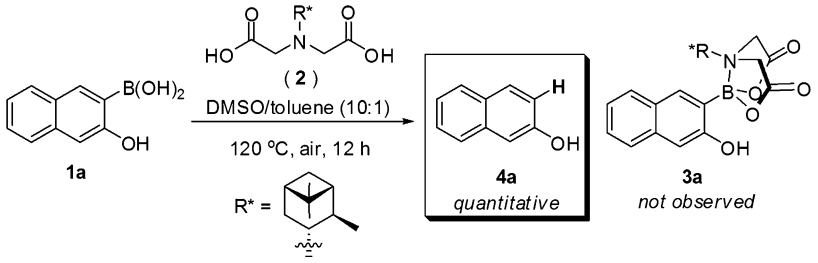
Scheme 2. Thermal Protodeboronation of 2-Naphthol Boronic Acid 1a

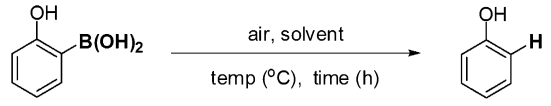


boronic acid with a chiral boron ligand and the subsequent Suzuki reaction of the resulting (*R*)- and (*S*)-BINOL boronic acid.[14] Continuing our research in the development of efficient methods for the preparation of axially chiral compounds, we attempted to synthesize chiral BINOL derivatives through the diastereoselective coupling reaction of 2-naphthol derivative **3a** bearing a chiral boronate at the 3-position and subsequent Suzuki reaction. Throughout our attempts to introduce pinene-derived iminodiacetic acid **2** (PIDA) into the boronic acid moiety of compound **1a** as a chiral boron ligand under the previously developed conditions,[15,16] no formation of PIDA boronate **3a** was observed; instead, an unexpected compound was formed as the sole product. Careful structural analysis showed that the unexpected product was 2-naphthol **4a**, presumably formed via thermal protodeboronation (Scheme 2).

Because protodeboronations of simple arene boronic acids are known to take place under relatively harsh conditions, such as in the presence of metal catalysts and/or strong acid/base at high temperatures,[9,13] and metal-free protodeboronations of arene boronic acids have not been previously described under neutral conditions even at high temperatures, we decided to investigate this unusual metal-free thermal protodeboronation of hydroxyarene boronic acids.

First, we attempted to prepare 2-hydroxyphenyl boronic acid **1b** as a model compound for protodeboronation studies by following a literature procedure.[17] Surprisingly, we were not able to obtain this compound in a pure form. Even more surprisingly, compound **1b** purchased from several commercial suppliers also contained similar impurities.[18] Without further purification of **1b**, we decided to subject **1b** to protodeboronation under the aforementioned reaction conditions. The protodeboronation proceeded smoothly, and phenol **4b** was obtained as the only product despite the presence of unidentifiable impurities in the starting boronic acid (Table 1, entry 1).[19] Initially, we suspected that PIDA **2** might play some role in protodeboronation. However, when the same reaction was performed in the absence of **2**, protodeboronation still occurred, leading to the conclusion that PIDA has no effect on the protodeboronation (Table 1, entry 2). The choice of solvent had a significant effect on the protodeboronation (Table 1, entries 2−6); the protodeboronation reaction proceeded in DMSO and DMF, whereas no apparent reaction was observed in other solvents. Because protodeboronation proceeded much faster in DMSO than in DMF, DMSO was selected as the solvent of choice. Reaction temperature had also a strong influence on the protodeboronation (Table 1, entries 2, 7−8). Protodeboronation progressed very slowly at 80 °C (Table 1, entry 7); an increase to 100 °C resulted in a more rapid reaction (24 h, quantitative; Table 1, entry 8), and further temperature increase to 120 °C promoted complete protodeboronation within 4 h (Table 1, entry 2). The reaction

Table 1. Investigation of Reaction Parameters



1b 4b

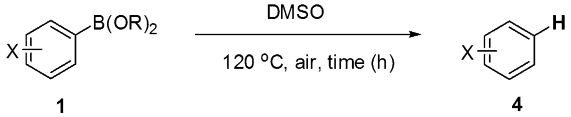
entry	solvent	temp. (°C)	time (h)	yield (%)[a]
1[b]	DMSO	120	4	100
2	DMSO	120	4	100
3	DMF	120	72	40
4	dioxane	120	24	N.R.[c]
5	toluene	120	24	N.R.[c]
6	*n*-BuOH	120	24	N.R.[c]
7	DMSO	80	24	20
8	DMSO	100	24	100
9[d]	DMSO	120	4	100
10[e]	DMSO	120	24	N.R.[c]

[a]Determined by ^{1}H NMR analysis. [b]1.5 equiv of PIDA **2** was used. [c]N.R., no reaction. [d]Under an argon atmosphere. [e]Reaction was conducted in the presence of 4 Å molecular sieves.

atmosphere had very little effect on the protodeboronation, as reaction under an inert atmosphere provided **4b** in similar yield as that conducted in air (Table 1, entries 2 and 9). Interestingly, water was found to play a very important role in protodeboronation: boronic acid **1b** remained intact in the presence of molecular sieves (Table 1, entry 10).

Under these conditions (DMSO, 120 °C, and open flask), we investigated the effect of substituent (X) on arene boronic acids **1** on the protodeboronation (Table 2). First, we investigated

Table 2. Effect of Substituents on the Protodeboronation



1 4

entry	1	$(OR)_2$	X	time (h)	yield (%)[a]
1	**1b**	$(OH)_2$	2-OH	4	100 (95)[b]
2	**1c**	$(OH)_2$	2-Me	24	N.R.[c]
3	**1b-Me**	$(OH)_2$	2-OMe	24	N.R.[c]
4	**1b-MOM**	$(OH)_2$	2-OMOM	24	N.R.[c]
5	**1b-Bn**	$(OH)_2$	2-OBn	24	N.R.[c]
6	**1d**	$(OH)_2$	3-OH	24	N.R.[c]
7	**1e**	$(OH)_2$	4-OH	12	100 (96)[b]
8	**1e-Me**	$(OH)_2$	4-OMe	24	trace[d]
9	**1b-pin**	pinacol	2-OH	24	100 (96)[b]
10	**1e-pin**	pinacol	4-OH	24	100 (94)[b]

[a]Determined by ^{1}H NMR analysis. [b]Yields in parentheses were isolated yields. [c]N.R., no reaction. [d]<5% yield.

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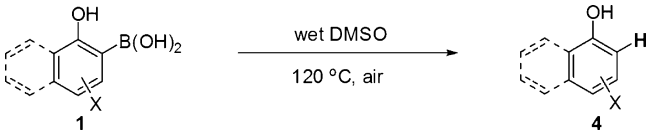
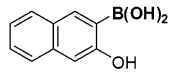
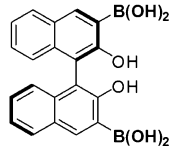
the influence of the type of substituent at the ortho position of boronic acids **1** on the protodeboronation (Table 2, entries 1–5). Interestingly, no arene boronic acids bearing substituents other than a hydroxyl group at the ortho position underwent the protodeboronation reaction. For example, ortho-toluene boronic acid **1c** did not undergo any protodeboronation reaction even after 24 h (Table 2, entry 2). Furthermore, when the hydroxyl group of boronic acid **1b** was protected as either the methyl, methoxymethyl (MOM), or benzyl groups, protodeboronation did not occur under the same conditions (Table 2, entries 1, 3–5). Next, we examined an effect of the position of the phenolic hydroxyl group in the phenyl ring on the protodeboronation. Positions of the phenolic hydroxyl group exhibited significant effects on the protodeboronation (Table 2, entries 1, 6, and 7). Boronic acids **1b** and **1e** bearing the hydroxyl group at the ortho and para positions, respectively, readily underwent the protodeboronation (Table 2, entries 1 and 7), whereas meta-phenol boronic acid **1d** remained unreacted even after a prolonged reaction time (Table 2, entry 6). Similar to ortho-phenol boronic acid **1b**, the presence of a free phenolic hydroxyl group of para-phenol boronic acid **1e** turned out to be critical for protodeboronation. When the hydroxyl group in **1e** was protected as the corresponding methyl ether, no protodeboronation occurred (Table 2, entry 8). We also investigated the effect of a free hydroxyl group at the boronic acid moiety on protodeboronation. When the boronic acid moieties in compounds **1b** and **1e** were converted into the corresponding pinacol boronates, **1b-pin** and **1e-pin**, protodeboronation still proceeded, albeit at slower rates (Table 2, entries 9 and 10).

With these results in hand, we investigated the generality of the protodeboronation reaction of ortho-hydroxyaryl boronic acids **1** bearing a substituent on the arene rings. Because many ortho-hydroxyaryl boronic acids are commercially available,[20] we purchased several ortho-hydroxyaryl boronic acids and attempted to subject them directly to the protodeboronation reaction (Table 3). When these commercially available compounds were subjected directly to protodeboronation under the optimized conditions without further purification, the corresponding phenols were obtained as the sole products regardless of the steric and electronic nature of phenol rings in boronic acids **1** (Table 3, entries 1–7). Furthermore, this protodeboronation reaction is not limited to simple phenol boronic acid derivatives and can be extended to fused aromatic systems. For example, 2-naphthol boronic acid **1a** bearing a hydroxyl group at the 3-position underwent protodeboronation to afford 2-naphthol **4a** (Table 3, entry 8). In addition, a chiral BINOL derivative **1l** bearing boronic acids at the 3,3′-positions smoothly underwent protodeboronation to provide (*R*)-BINOL (Table 3, entry 9).

With these results in hand, we attempted to develop novel synthetic methods using this protodeboronation of phenol boronic acids. Although EAS reactions of phenols have been used extensively to prepare functionalized phenols, EAS reactions in general afford the para-functionalized phenols. Thus, we first attempted to develop a protocol for the synthesis of ortho-functionalized phenols by using a boronic acid moiety as a blocking group in EAS reactions followed by the removal of the boronic acid moiety through protodeboronation. Unfortunately, when **1e** was treated with *N*-bromosuccimide (NBS), bromodeboronation took place to afford 4-bromophenol **4k** in quantitative yield (Scheme 3, eq 1).[21] However, when the corresponding pinacol boronate **1e-pin** was used instead, the

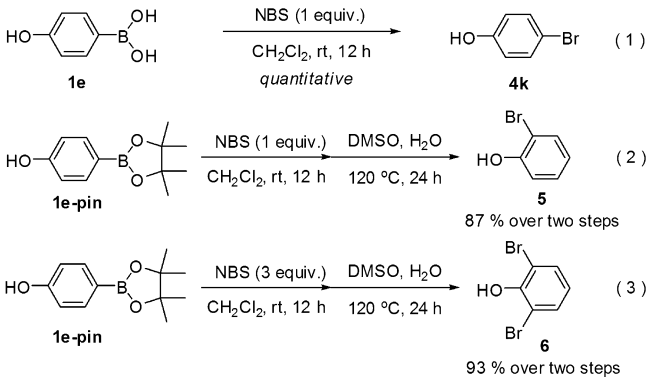
Table 3. Substrate Scope[a]



entry	boronic acid (**1**)	time (h)	yield (%)[b]
1	**1b** : X = Y = H	4	95
2	**1f** : X = OMe, Y = H	12	93
3	**1g** : X = Me, Y = H	24	96
4	**1h** : X = F, Y = H	18	91
5	**1i** : X = H, Y = F	18	94
6	**1j** : X = H, Y = Cl	18	95
7	**1k** : X = H, Y = Br	18	92
8	 **1a**	18	98
9	 **1l**	24	94

[a]Reaction conditions: ortho-hydroxyaryl boronic acid **1** (0.20 mmol), DMSO (1.0 mL), 120 °C, open flask. [b]Isolated yields.

Scheme 3. ortho Functionalization of Phenols Using a Boronic Acid Moiety as a Blocking Group



bromodeboronation could be avoided and bromination took place only at the ortho position of phenol to afford 2-bromophenol **5** in 87% yield after the removal of the boronic acid moiety (Scheme 3, eq 2).[22] Furthermore, when an excess of NBS (>2 equiv) was used, bromination took place only at the ortho position, and no bromodeboronation was observed even in the presence of remaining NBS. After the removal of boronic acid, 2,6-dibromophenol **6** was obtained in excellent yield (Scheme 3, eq 3).

With the successful application of a boronic acid moiety as a blocking group in the EAS reactions, we attempted to develop further the meta functionalization of phenols using boronic acid as a directing group[7,8] and the subsequent protodeboronation. For example, a removable directing group (RDG) introduced into boronic acid **1e** could lead to ortho-functionalization to afford an ortho-functionalized boronic acid **8**. Removal of both RDG and the boronic acid moiety would eventually provide a meta-functionalized phenol (Scheme 4).

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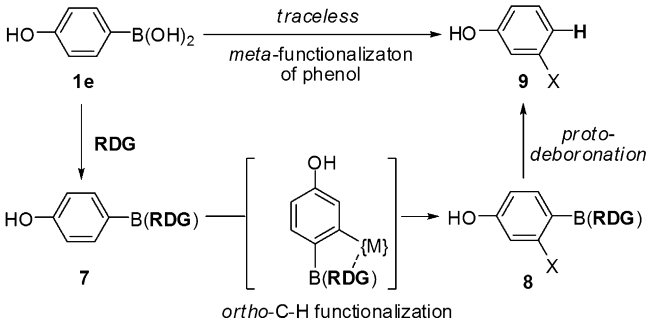
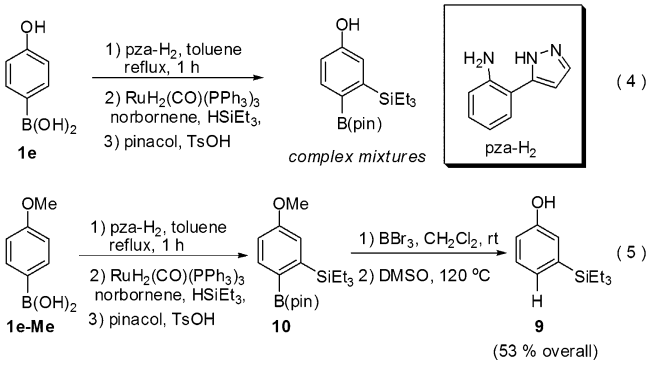
Scheme 4. Traceless meta Functionalization of Phenols



Based on this idea, we attempted to prepare a meta-functionalized phenol directly from **1e** using 2-pyrazol-5-ylaniline (pza) as a removable directing group (RDG), which was developed by the Suginome group,[7] on the boron atom. However, **1e** did not provide the desired product; instead complex mixtures were obtained (Scheme 5, eq 4). Because

Scheme 5. meta Functionalization of Phenols Using a Boronic Acid Moiety as a Directing Group

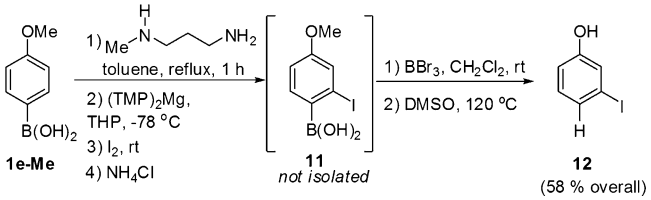


complications in the pza-directed ortho functionalization might be ascribed to the free hydroxyl group in **1e**, we decided to use a protected phenol boronic acid **1e-Me** instead. To our delight, the ortho-directed silylation proceeded smoothly to provide the corresponding pinacol boronate **10** in 75% yield over three steps. Deprotection with BBr_3 and subsequent thermal protodeboronation afforded meta-silylated phenol **9** in 93% yield (Scheme 5, eq 5). Furthermore, **9** could be obtained with similar efficiency (53% over five steps) from **1e-Me** through pza-directed ortho functionalization without isolation of intermediate **10**.

Furthermore, meta functionalization of phenols could be demonstrated through the ortho-metalation of the boronic acid moiety in **1e-Me** followed by trapping with an electrophile. Subsequent deprodection and protodeboronation could afford a meta-functionalized phenol. Reaction of **1e-Me** with $(TMP)_2Mg$ (TMP═2,2,6,6-tetramethylpiperidine) using *N*-methyl-1,3-propanediamine as an RDG and subsequent trapping with I_2 afforded ortho-iodoborylated intermediate **11**.[8] Without isolation of **11**, deprotection with BBr_3 and subsequent protodeboronation yielded meta-iodophenol **12** in 58% (Scheme 6).

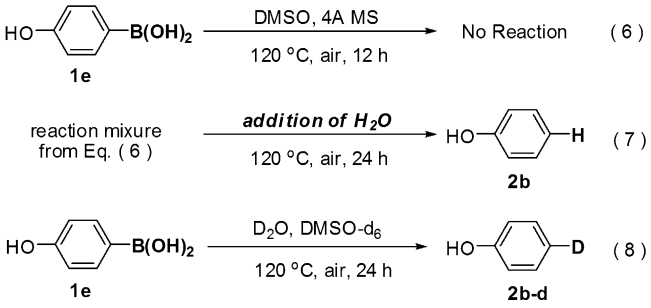
With these results in hand, we endeavored to elucidate the reaction mechanism for this protodeboronation. During the optimization of reaction conditions, we found that the presence of water exhibited a significant effect on the protodeboronation

Scheme 6. Synthesis of meta Iodophenol via a Boronic Acid-Directed Functionalization



of **1b** (Table 1, entry 10). Thus, we decided to investigate the effect of water on the protodeboronation (Scheme 7). When

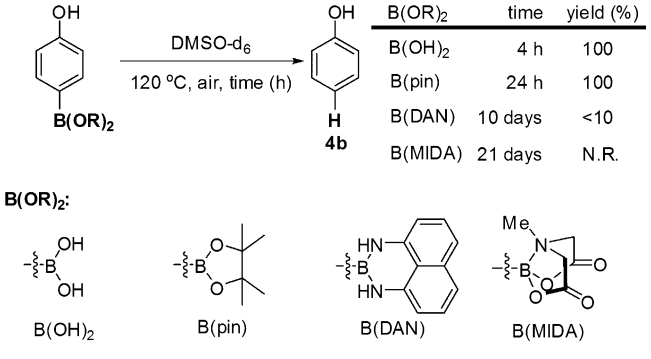
Scheme 7. Effect of Water on the Protodeboronation of 1e



the protodeboronation of **1e**[23] was performed in the presence of molecular sieves, no significant reaction was observed even after a long reaction time (Scheme 7, eq 6). Moreover, upon the addition of a small amount of water to the above mixture in eq 6, protodeboronation again proceeded to afford phenol **2b** in quantitative yield (Scheme 7, eq 7). Furthermore, when the reaction was carried out in the presence of D_2O, deuterium was incorporated in the carbon originally connected to the boron atom (Scheme 7, eq 8).

In addition, it was also found that the corresponding pinacol boronate **1e-pin** displayed significantly lower reactivity than the parent boronic acid **1e** in the protodeboronation reaction (Table 2, entries 7 and 10). From these results, we envisaged that the Lewis acidity on the boron atom might play a role in the protodeboronation. Thus, several boronates possessing different Lewis acidities were prepared,[24] and their reactivities toward protodeboronation were investigated (Scheme 8). Interestingly, the attenuation of the Lewis acidity on the boron significantly slowed the protodeboronation. For example, DAN boronate from **1e** bearing low Lewis acidity underwent

Scheme 8. Protodeboronation of Boronates Bearing Different Lewis Acidities



B(OR)$_2$	time	yield (%)
B(OH)$_2$	4 h	100
B(pin)	24 h	100
B(DAN)	10 days	<10
B(MIDA)	21 days	N.R.

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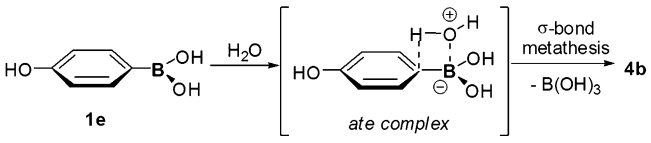
minimal protodeboronation at 120 °C even after 10 days. Furthermore, the corresponding MIDA boronate remained intact even after 3 weeks under the standard conditions for protodeboronation.

On the basis of these results, we believed that the protodeboronation reaction might proceed via a two-step sequence (Scheme 9): the water coordinates to the boron atom in a boronic acid moiety to form an ate complex and subsequent σ-bond metathesis provides the corresponding phenol and a boric acid.

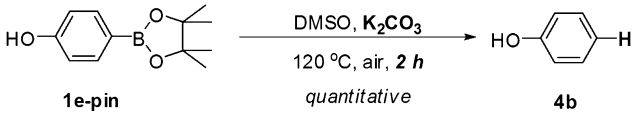
Scheme 9. Proposed Reaction Mechanism for Protodeboronation[a]



[a]A similar mechanism could be applied to ortho-phenol boronic acid **1b**.

This proposed reaction mechanism could explain the unique reactivity of ortho- and para-phenol boronic acids on protodeboronation. The higher reactivity of ortho- and para-phenol boronic acids compared with meta-phenol boronic acid could be explained based on the partial ionization of these phenol boronic acids, which would further increase electron density at the ortho and para positions of the phenol ring. Along this line, a strong solvent dependence on reactivity might also support such a partial ionization of the phenolic hydroxy group.[25] To test this idea, we actually prepared an ionized form of **1e-pin** and compared its reactivity with that of the parent **1e-pin** (Scheme 10). When **1e-pin** was subjected to protodeboronation in the presence of K_2CO_3, delightfully, protodeboronation was complete within 2 h. This result clearly demonstrated that ionization of phenol significantly enhanced the reactivity for protodeboronation of *para*-phenol boronic acid.

Scheme 10. Protodeboroantion of 1e-pin in the Presence of K_2CO_3



In conclusion, we have reported the first metal-free thermal protodeboronation of arene boronic acids bearing a hydroxyl group at the ortho and para positions relative to the boronic acid moiety in DMSO under neutral conditions. Under these conditions, various ortho- and para-phenol boronic acids underwent protodeboronation to afford the corresponding phenol derivatives in excellent yields. Furthermore, we have developed a novel protocol for exclusive ortho and meta functionalization of phenols using a boronic acid moiety as a blocking group and a directing group, respectively, followed by the removal of the boronic acid moiety via protodeboronation. Mechanistic studies suggested that protodeboronation proceeds through coordination of water to the boron atom on the boronic acid followed by σ-bond metathesis.

EXPERIMENT SECTION

General. All reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography (TLC) using precoated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm) with a combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed according to the method of Still using silica gel 60 (230–400 mesh). Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted. All hydroxy arene boronic acids **1** were purchased from commercial suppliers. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 and 100 MHz NMR spectrometers, respectively. Tetramethylsilane and the solvent resonance were used as internal standards for ^{1}H NMR (δ 0.0 ppm) and ^{13}C NMR, respectively. The proton spectra are reported as follows δ (position of proton, multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet), and br (broad). High-resolution mass spectra (HRMS) were obtained using quadrupole instrument with FAB as the ionization method.

General Procedure for Protodeboronation of ortho-Phenol Boronic Acid Derivatives ***1*** *(Table 3).* A solution of arene boronic acid **1** (0.20 mmol) in either DMSO or DMSO-d_6 (1.0 mL) was stirred at 120 °C. The reaction mixture was monitored by TLC and ^{1}H NMR. After complete consumption of boronic acid **1** by TLC and/or ^{1}H NMR analysis, the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with ether. The organic layer was combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (hexanes/EtOAc 5:1) to afford the corresponding phenol derivative **4**.

*2-Naphthol (**4a**).* The spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 28 mg, 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.73 (m, 2H), 7.66 (d, J = 8.24 Hz, 1H), 7.42 (t, J = 7.42 Hz), 7.32 (t, J = 7.14 Hz), 7.13–7.07 (m, 2H), 5.14 (s, 1H).

*Phenol (**4b**).* The spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 18 mg, 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, J = 7.83 Hz, 2H), 6.93 (t, J = 7.43 Hz, 1H), 6.83 (d, J = 7.83 Hz, 2H), 5.39 (br, 1H).

*2-Methoxyphenol (**4f**).* The spectroscopic data were in good agreement with the literature.[27] Yield: 23 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.69 (m, 4H), 5.68 (br, 1H), 3.86 (s, 3H).

*2-Methylphenol (**4g**).* The spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 21 mg, 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (br, 1H), 7.03–6.93 (m, 2H), 6.74 (d, J = 7.69 Hz, 1H), 6.65 (t, J = 7.28 Hz), 5.16 (br, 1H), 2.09 (s, 3H).

*2-Fluorophenol (**4h**).* The spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 20 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–6.84 (m, 4H), 5.15 (br, 1H).

*4-Fluorophenol (**4i**).* The spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 21 mg, 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 –6.75 (m, 4H), 5.05 (br, 1H).

*4-Chlorophenol (**4j**).* The spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 24 mg, 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.61 Hz, 2H), 6.77 (d, J = 8.61 Hz, 2H), 5.13 (br, 1H).

*4-Bromophenol (**4k**).* The spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 32 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.22 Hz, 2H), 6.71 (d, J = 8.22 Hz, 2H), 5.16 (br, 1H).

*(R)-2,2′-Dihydroxy-1,1′-dinaphthyl (**4l**).* The spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 54 mg, 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.79 Hz, 1H),

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7.90 (d, J = 7.97 Hz, 1H), 7.40−7.28 (m, 6H), 7.16 (d, J = 8.79 Hz, 2H), 5.04 (s, 3H).

General Procedures for ortho Functionalization of Phenols. To a solution of **1e-pin** (0.44 g, 2.0 mmol; 1.0 equiv) in CH_2Cl_2 (10 mL) was added NBS (1.0 or 3.0 equiv). The reaction mixture was stirred at room temperature and monitored by TLC. After complete consumption of **1e-pin**, the reaction mixture was quenched with water and extracted with EtOAc (3 × 30 mL). The organic layer was combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was directly subjected to protodeboronation without further purification. The residue obtained above was dissolved in DMSO (10 mL) and H_2O (2 mL). The reaction mixture was stirred at 120 °C and monitored by TLC. After complete consumption of the resulting boronate, the reaction mixture was cooled to room temperature and extracted with ether. The organic layer was combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (hexanes/EtOAc 5:1).

*2-Bromophenol (**5**).* Reaction with 1.0 equiv of NBS (0.36 g, 2.0 mmol). Compound **5** was obtained as colorless oil, and the spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 0.30 g, 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, J = 8.10, 1.24 Hz, 1H), 7.22 (t, J = 7.69 Hz, 1H), 7.02 (dd, J = 8.10, 1.24 Hz, 1H), 6.80 (t, J = 7.69 Hz, 1H), 5.52 (br, 1H).

In addition, the ^{1}H NMR of the crude mixture showed that there was a trace amount of dibrominated compound.

*2,6-Dibromophenol (**6**).* Reaction with 3.0 equiv of NBS (1.1 g, 6.0 mmol). Compound **6** was obtained as a white solid, and the spectroscopic data were in good agreement with a commercially available sample.[26] Yield: 0.46 g, 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 7.97 Hz, 2H), 6.71 (t, J = 7.97 Hz, 1H), 5.89 (br, 1H).

*General Procedure for Synthesis of meta-Silylated Phenol **9** via ortho-Boryl Directed C−H Activation followed by Protodeboronation:*[7] A mixture of boronic acid **1e-Me** (0.23 g; 1.5 mmol) and 2-pyrazol-5-ylaniline (pza, 0.24 g; 1.5 mmol) in toluene (6.0 mL) was heated under reflux with a Dean−Stark condenser for 1 h. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. To the residue was added $RuH_2(CO)(PPh_3)_3$ (83 mg; 0.090 mmol). Then, norbornene (0.71 g; 7.5 mmol), triethylsilane (0.87 g; 7.5 mmol), and toluene (2.0 mL) were added under an argon atmosphere. The reaction mixture was heated at 135 °C for 12 h. The reaction mixture was cooled to room temperature. The crude mixture was converted to the corresponding pinacol ester by adding pinacol (0.35g; 3.0 mmol), *p*-toluenesulfonic acid monohydrate (57 mg, 0.15 mmol), and THF (5.0 mL) at room temperature. The reaction mixture was allowed to stir for additional 3 h, quenched with water (10 mL), and extracted with EtOAc (10 mL × 3). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica (hexanes/EtOAc 10:1) to afford compounds **10**. The spectroscopic data were in good agreement with the literature.[28] Yield: 0.39 g, colorless oil, 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.24 Hz, 1H), 7.12 (d, J = 2.75 Hz, 1H), 6.84 (dd, J = 8.24, 2.75 Hz, 1H), 3.82 (s, 3H), 1.33 (s, 12H), 0.92 (s, 15H).

Compound **10** was dissolved in dichloromethane (10 mL) and treated with BBr_3 (0.28 mL, 0.75 g; 3.0 mmol; 2.0 equiv) at 0 °C, and the reaction mixture was warmed to room temperature. After 12 h, the reaction was quenched with water (20 mL), and the aqueous layer was extracted with dichloromethane (20 mL × 3). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in DMSO (1.5 mL) and H_2O (0.1 mL). The reaction mixture was stirred at 120 °C and monitored by TLC. After complete protodeboronation, the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with ether. The organic layer was combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (hexanes/EtOAc 5:1). The spectroscopic data were in good agreement with the literature.[29] Yield: 0.17 g, colorless oil, 53%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, J = 7.42 Hz, 1H), 7.06 (d, J = 7.14 Hz, 1H), 6.95 (d, J = 2.20 Hz, 1H), 6.82 (dd, J = 7.97, 1.92 Hz, 1H), 0.96 (t, J = 7.55 Hz, 9H), 0.81−0.73 (m, 6H).

When the crude mixture of compound **10** could be directly applied to the protodeboronation without further purification, compound **9** was obtained in comparable yield as that above.

*General Procedure for Synthesis of meta-Iodophenol **12** via ortho-Boryl Directed Metalation and Trapping with I_2 followed by Protodeboronation.*[8] *Preparation of $(TMP)_2Mg$.* *n*-BuLi (10 mL, 25 mmol, 2.5 M in hexanes) was added dropwise to a solution of TMPH (4.2 mL, 25 mmol) in THP (25 mL) at −78 °C, and the reaction mixture was stirred at −20 °C for 30 min to give THPLi. To the above solution was added $MgBr_2{\cdot}OEt_2$ (3.23 g, 12.5 mmol) in several portions at −78 °C over 10 min. Then the reaction mixture was stirred at 0 °C for 2 h to produce $(TMP)_2Mg$ in THP.

*Synthesis of meta-Iodo Phenol (**12**).* A solution of **1e-Me** (2.0 g, 9.8 mmol) and *N*-methyl-1,3-diaminopropane (1.05 mL, 10.1 mmol) in toluene (100 mL) was refluxed with azeotropic removal of water using a Dean−Stark condenser for 4 h. Then, the solvent was removed under reduced pressure to afford the crude mixture. The crude mixture was subjected to bulb-to-bulb distillation to yield the resulting boronate bearing an RDG. The resulting boronate was directly used for the netx step. A solution of the boronate bearing an RDG obtained above was added to the solution of $(TMP)_2Mg$ in THP prepared above at 0 °C. Then, the reaction mixture was stirred at room temperature for 30 min and refluxed for additional 2 h. Then, the reaction mixture was cooled to room temperature and treated with a solution of I_2 (15 g, 58.8 mmol) in THF (200 mL) and warmed to room temperature with stirring overnight. The crude diaminoborane was obtained as residue after evaporation of the solvents. To the residue was added saturated NH_4Cl (10 mL). The white suspension of the reaction mixture was stirred at room temperature for 1 day. Then, the reaction mixture was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated to afford the crude residue of **11**. Compound **11** was subjected to deprotection and protodeboronation without further purification. BBr_3 (1.9 mL, 20 mmol) was added dropwise to the crude residue of **11** obtained above in dichloromethane (100 mL) at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layer was combined and concentrated. The residue was dissolved in DMSO (20 mL), and H_2O (1.0 mL) was added to the reaction mixture. The reaction mixture was allowed to stir at 120 °C in an open flask for 24 h. After the protodeboronation was completed, the reaction mixture was quenched with H_2O, extracted with EtOAc, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica (hexanes/EtOAc 4:1) to afford meta-iodo phenol **12**. The spectroscopic data were in good agreement with the literature.[29] Yield: 1.3 g, colorless oil, 58% over six steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.20 (m, 2H), 6.95 (t, J = 7.97 Hz, 1H), 6.80 (dd, J = 8.24, 1.92 Hz, 1H), 5.66 (br, 1H).

General Procedure for Preparation of 4-Phenol Boronates Bearing Lower Lewis Acidity. A solution of (4-hydroxyphenyl)boronic acid **1e** (0.14 g, 1.0 mmol), 1,8-diaminonaphthalene (0.24 g, 1.5 mmol), and molecular sieves (4 Å, 50 mg) in a mixture of DMSO and toluene (1:10, 3 mL) was refluxed with azeotropic removal of water using a Dean−Stark condenser under an air atmosphere. After 12 h, the reaction mixture was cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (20 mL). The organic layer was combined, washed with brine (20 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/hexanes (1:1).

DAN-boronate.[30] Yield: 0.25g, red solid, 96%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.65 (br, 1H), 8.11 (s, 2H), 7.76 (d, J = 8.24 Hz, 2H), 7.06 (t, J = 7.83 Hz, 2H), 6.87 (d, J = 7.97 Hz, 2H), 6.81 (d, J = 8.52 Hz, 2H), 6.56 (d, J = 7.69 Hz, 2H).

MIDA-boronate.[25] Yield: 0.23 g, 94%. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.42 (br, 1H), 7.22 (d, J = 8.24 Hz, 2H), 6.74 (d, J = 8.24 Hz, 2H), 4.31−4.02 (dd, J = 72 Hz, J = 18 Hz, 4H), 2.46 (s, 3H).

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■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data for phenol derivatives **4**–**6**, **9**, **10**, and **12** as well as para-phenol boronates with lower Lewis acidity. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) We believed that the impurities might be intermediates in the course of protodeboronation, which is responsible for the formation of phenol **4b** as the sole product even though starting boronic acid **1b** contains impurities.

(20) On the basis of a SciFinder substructure search using ortho-hydroxyphenl boronic acid, more than 100 ortho-phenol boronic acid derivatives, including boronic acids in Table 2, are commercially available as of August 2013.

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(24) For the preparation of DAN and MIDA boronates, see the Supporting Information. The preparation of MIDA boronates from **1b** and **1e** will be reported in due course.

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