JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Metal-Free Protodeboronation of Electron-Rich Arene Boronic Acids and Its Application to *ortho*-Functionalization of Electron-Rich Arenes Using a Boronic Acid as a Blocking Group

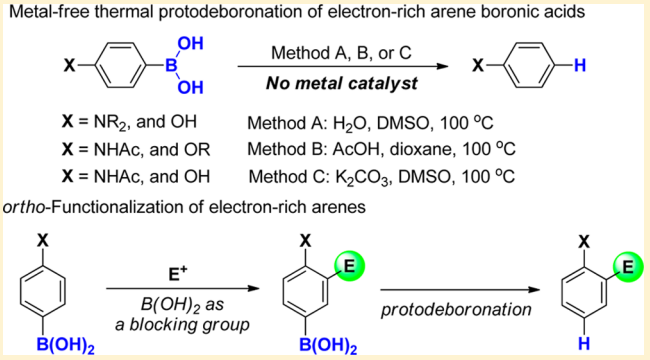
Su-Jin Ahn,[†] Chun-Young Lee,[†] Nak-Kyoon Kim,[‡] and Cheol-Hong Cheon*[,†]

[†]Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 136701, Republic of Korea

[‡]Advanced Analysis Center, Korea Institute of Science and Technology, 14-5 Hwarangro, Seongbuk-gu, Seoul 136791, Republic of Korea

Supporting Information

ABSTRACT: The metal-free thermal protodeboronation of various electron-rich arene boronic acids was studied. Several reaction parameters controlling this protodeboronation, such as solvent, temperature, and a proton source, have been investigated. On the basis of these studies, suitable reaction conditions for protodeboronation of several types of electron-rich arene boronic acids were provided. On the basis of this protodeboronation, a new protocol for the synthesis of *ortho*-functionalized electron-rich arenes from these boronic acids was developed using the boronic acid moiety as a blocking group in the electrophilic aromatic substitution reaction, followed by the removal of the boronic acid moiety via thermal protodeboronation. Mechanistic studies suggested that this protodeboronation might proceed via the complex formation of a boronic acid with a proton source, followed by the carbon−boron bond fission through σ-bond metathesis, to afford the corresponding arene compound and boric acid.



INTRODUCTION

Boronic acids and their derivatives have been employed as valuable intermediates in organic synthesis, particularly in transition-metal-catalyzed cross-coupling reactions, such as Suzuki−Miyaura and Chan−Lam reactions, due to their unique reactivity and low toxicity.[1] Unlike other organometallic compounds used in transition-metal-catalyzed cross-coupling reactions, boronic acids are generally believed to be stable and can be stored under ambient conditions, which makes a number of boronic acids currently commercially available.[2] However, the actual stability of boronic acids has been seldom investigated, and some of the boronic acids are not stable even though they are commercially available.[3]

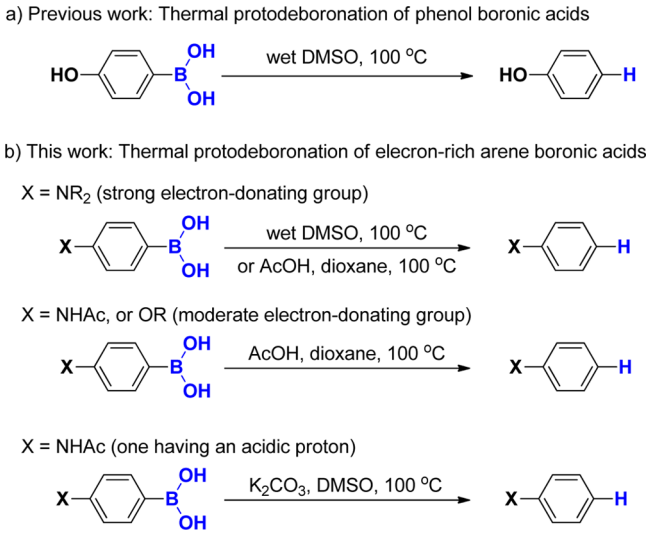
Protodeboronation of boronic acids,[4] the conversion of a carbon−boron bond in a boronic acid into a carbon−hydrogen bond, has been frequently observed in metal-catalyzed coupling reactions as one of the common side reactions. In addition, although protodeboronation is considered one of the possible decomposition pathways of unstable boronic acids,[5] the protodeboronation in the absence of a metal catalyst has been poorly investigated. Furthermore, the general, but a little biased, belief of the stability of boronic acids and the poor understanding of the reaction parameters controlling protodeboronation make the synthetic community reluctant to the development of viable synthetic methods using the protodeboronation.[6]

We recently found that *ortho*- and *para*-phenol boronic acids are not stable and readily undergo thermal protodeboronation in wet DMSO without any assistance of metal and/or acid additives (Scheme 1a).[7] With this rather unexplored metal-free thermal protodeboronation of *ortho*- and *para*-phenol boronic acids, we were curious whether this type of metal-free thermal protodeboronation might be a general behavior of not only phenol boronic acids but also other electron-rich arene boronic acids. In this present study, we would like to present our studies on metal-free thermal protodeboronation of electron-rich arene boronic acids (Scheme 1b).[8] After investigating the reaction parameters controlling this protodeboronation, we provided suitable reaction conditions for the protodeboronation of several types of electron-rich arene boronic acids carrying a different substituent on the arene ring system. In addition, a new protocol for the synthesis of stable surrogates for these unstable electron-rich arene boronic acids was developed. Furthermore, we successfully developed a new synthetic method for the *ortho*-functionalized electron-rich arenes using the boronic acid moiety as a blocking group in electrophilic aromatic substitution (EAS) reactions.[9,10] Mechanistic studies suggested that an electron-rich arene boronic acid would undergo protodeboronation reaction through the ate complex

Received: April 6, 2014
Published: July 22, 2014

   dx.doi.org/10.1021/jo500780b | J. Org. Chem. 2014, 79, 7277−7285

Scheme 1. Metal-Free Thermal Protodeboronation of Electron-Rich Arene Boronic Acids under Various Reaction Conditions

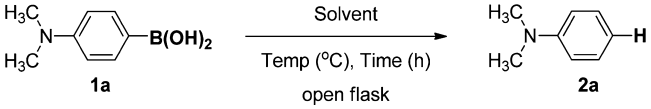


formation by coordination of a proton source with the boron atom in a boronic acid and subsequent σ-bond metathesis in the ate complex.

RESULTS AND DISCUSSION

We first investigated reaction parameters controlling the protodeboronation of electron-rich arene boronic acids in the absence of metal catalysts using commercially available 4-(*N*,*N*-dimethylamino)phenyl boronic acid **1a** as a model compound (Table 1). Since our previous studies on the metal-free thermal protodeboronation of *ortho*- and *para*-phenol boronic acids showed strong solvent dependence,[7] we first examined the effect of solvent on the protodeboronation of **1a**. Similar to our previous studies, it was found that the choice of solvent had a significant influence on the protodeboronation of **1a**. Boronic acid **1a** rapidly underwent protodeboronation in DMF and DMSO, leading to the corresponding aniline **2a** in quantitative yield (entries 1 and 2), whereas no protodeboration took place in any other solvent (entries 3−5). Next, the effect of reaction temperature was examined; the rate of the protodeboronation of **1a** was found to increase with the reaction temperature. For instance, protodeboronation was completed in 2 h at 100 °C, while **1a** was more rapidly converted into **2a** at 120 °C in both DMSO and DMF (entries 6 and 7). In addition, water was found to have a significant effect on the protodeboronation. The protodeboronation of **1a** much more slowly proceeded in the presence of molecular sieves, in other words, in the absence of water, and the protodeboronation was completed after 48 h (entry 8).

Table 1. Investigation of Reaction Parameters

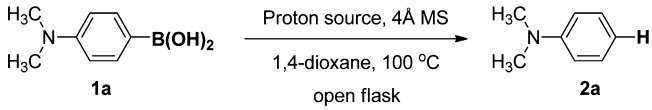


entry	solvent	temp (°C)	time (h)	yield[a] (%)
1[b]	DMSO	100	2	100
2	DMF	100	8	100
3	1,4-dioxane	100	48	N.R.[c]
4	H_2O	100	48	N.R.[c]
5	EtOH	80	48	N.R.[c]
6	DMSO	120	0.5	100
7	DMF	120	1.5	100
8[d]	DMSO	100	48	100

[a]Determined by ^{1}H NMR of the crude mixture. [b]DMSO-d_6 was used. [c]No reaction. [d]Conducted in the presence of 4 Å molecular sieves.

Since water turned out to have a profound effect on the protodeboronation of not only phenol boronic acid but also aniline boronic acid, we investigated the effect of other external proton sources on the protodeboronation of **1a** (Table 2). In order to investigate the sole effect of an external protic acid on protodeboronation of **1a**, we decided to use 1,4-dioxane as the solvent of choice to exclude the protodeboronation with residual water in the solvent. Interestingly, the rate of protodeboronation of **1a** increased with the acidity of an external proton source.[11] When an external proton source having a similar acidity with water was used, no protodeboronation was observed even after 48 h (entries 1−4). However, when hexafluoroisopropanol (HFIP) and acetic acid were used as external proton sources, respectively, boronic acid **1a** was completely converted into the corresponding aniline **2a** (entries 5 and 6). Rather unexpectedly, when much stronger Brønsted acidic trifluoroacetic acid (TFA) was used as an external proton source, no protodeboronation product **2a** was observed and a complex mixture was obtained (entry 7). This was presumably due to direct protonation of TFA on the nitrogen at the amino group in **1a**, leading to other reaction pathways than the protodeboronation.

Table 2. Effect of Proton Sources



entry	proton source	pK_a	time (h)	yield[a] (%)
1	2-propanol	16.5	48	N.R.[b]
2	ethanol	15.7	48	N.R.[b]
3	methanol	15.5	48	N.R.[b]
4	H_2O	15.7	48	N.R.[b]
5	HFIP	9.3	6.5	100
6	AcOH	4.76	0.5	100
7	TFA	−0.25	5	[c]

[a]Determined by ^{1}H NMR of the crude mixture. [b]No reaction. [c]Complex mixture was obtained.

With these results in hand, we explored the effect of a substituent in an arene boronic acid on the protodeboronation (Scheme 2). Interestingly, a substituent at the *para*-position to the boronic acid moiety showed a strong influence on the reactivity of protodeboronation. When *para*-toluene boronic acid derivatives **1b** and **1c** were subjected to the above conditions (Methods A and B), no protodeboronation reaction was observed. Furthermore, when TFA was used as an external proton source in the protodeboronation of **1b** and **1c** at the elevated temperature (Method D), they did not undergo the protodeboronation. These results implied that toluene boronic acid derivatives are stable toward this metal-free thermal protodeboronation reaction. Next, the protodeboronation of anisole boronic acid derivatives **1d−f** was examined. All anisole boronic acids **1d−f** did not undergo any protodeboronation in

dx.doi.org/10.1021/jo500780b | J. Org. Chem. 2014, 79, 7277−7285

Scheme 2. Protodeboronation of Various Electron-Rich Arene Boronic Acids 1

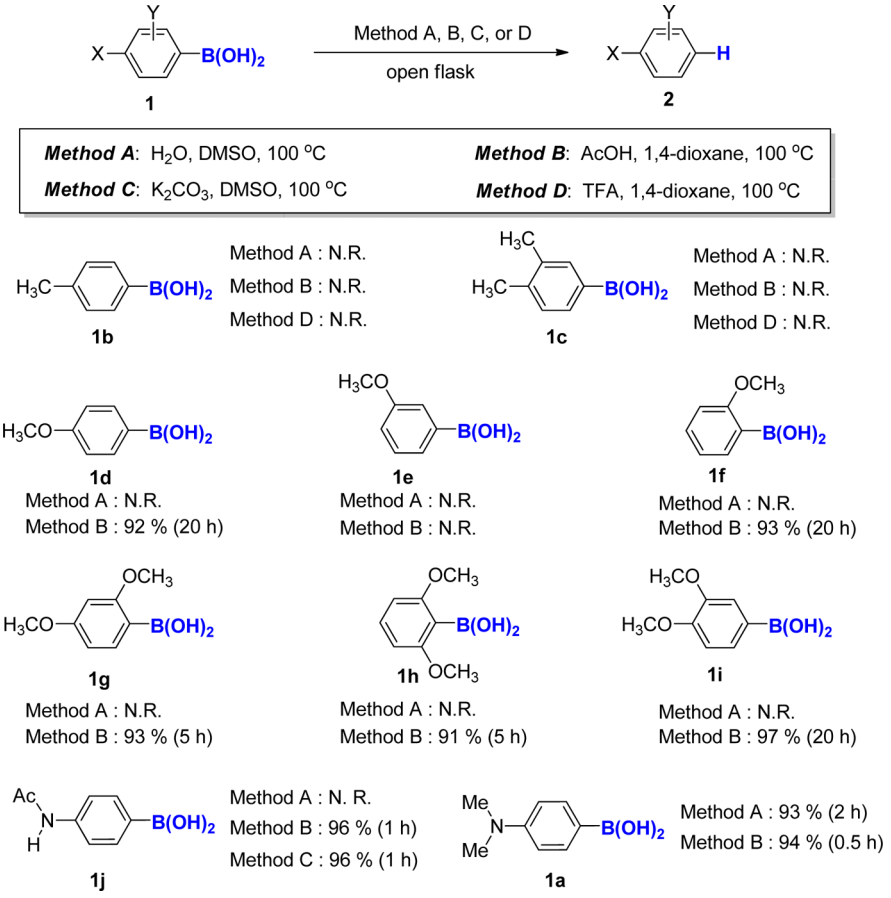


Table 3. Summary of Protodeboronation Conditions for Various Arene Boronic Acids[a,b,c,d,e]

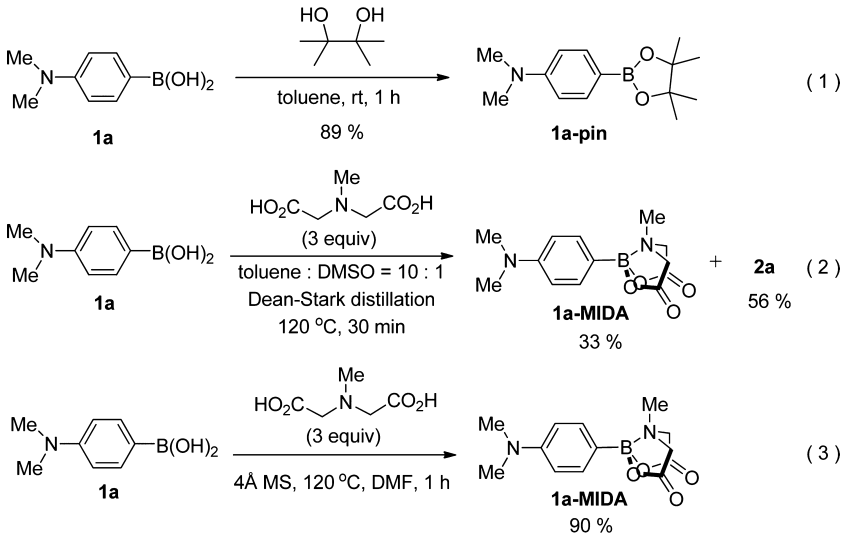
		Conditions[a]		
entry	Boronic Acid **1**	Method A	Method B	Method C
1	Me, $B(OH)_2$	N.R.[b]	N.R.[b]	N.D.[c]
2	MeO, $B(OH)_2$	N.R.[b]	C.P.[d]	N.D.[c]
3	AcHN, $B(OH)_2$	N.R.[b]	C.P.[d]	C.P.[d]
4[e]	HO, $B(OH)_2$	C.P.[d]	C.P.[d]	C.P.[d]
5	Me_2N, $B(OH)_2$	C.P.[d]	C.P.[d]	N.D.[c]

[a]Conditions: Method A (H_2O, DMSO, 100 °C); Method B (AcOH, dioxane, 100 °C); Method C (K_2CO_3, DMSO, 100 °C). [b]No reaction. [c]Not determined. [d]C.P. means complete protodeboronation to provide the corresponding arene compound **2** in quantitative yield. [e]For the protodeboronation of *para*-phenol boronic acid, see ref 8.

wet DMSO (Method A), whereas the protodeboronation smoothly took place under the conditions where acetic acid was used as an external proton in dioxane at 100 °C (Method B). Similar to our previous report on the protodeboronation of phenol boronic acids,[7] the position of the methoxy group to the boronic acid moiety had a significant influence on the reactivity in the protodeboronation. *ortho*- and *para*-anisole boronic acids **1d** and **1f** underwent complete protodeboronation after 20 h, whereas no protodeboronation was observed with *meta*-anisole boronic acid **1e**. Furthermore, the introduction of additional substituents on the arene ring in these boronic acids increased the reactivity for the protodeboronation; anisole boronic acids **1g**−**1i** carrying an additional methoxy substituent on the arene ring system displayed much higher reactivity toward proto-

dx.doi.org/10.1021/jo500780b | J. Org. Chem. 2014, 79, 7277−7285

Scheme 3. Preparation of Stable Surrogates for 1a



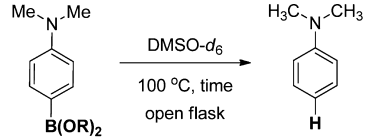
deboronation to afford the protodeboronation products in quantitative yields in a much shorter reaction time. Next, we examined the protodeboronation of anilide boronic acid derivatives. When anilide boronic acid **1j** was subjected to the protodeboronation reaction under the conditions for Method A, protodeboronation did not occur. However, **1j** rapidly underwent protodeboronation with acetic acid as a proton source to afford the corresponding anilide **2j** in quantitative yield (Method B). Similar to *para*-phenol boronic acid bearing an acidic proton on the substituent, the protodeboronation of **1j** also took place under basic conditions (Method C).[7,12] Finally, aniline boronic acid derivatives, such as **1a**, displayed much higher reactivity than other electron-rich arene boronic acids and readily underwent protodeboronation using either Method A or Method B.

On the basis of these results, we established the conditions for the protodeboronation of several types of electron-rich arene boronic acids carrying different substitutents (Table 3). In order to preclude the steric effect on the protodeboronation, we utilized arene boronic acids bearing substituents at the *para*-position to the boronic acid moiety. The protodeboronation showed a proportional relationship with the electron-donating ability of the substituent at the *para*-position.[13] Alkyl substituted phenyl boronic acids, such as *para*-toluene boronic acid **1b**, turned out to be stable toward this metal-free thermal protodeboronation reaction (entry 1). Although *para*-anisole boronic acid **1d** and *para*-anilide boronic acids **1j** did not undergo protodeboronation using water as a proton source in DMSO (Method A), protodeboronation of these boronic acids took place with acetic acid in dioxane (Method B) (entries 2 and 3). On the other hand, *para*-phenol boronic acid and *para*-aniline boronic acid **1a** displayed much higher reactivity and readily underwent protodeboronation in wet DMSO at elevated temperature (entries 4 and 5). In addition, boronic acids bearing an acidic proton on the *para*-substituent, such as *para*-phenol and *para*-anilide boronic acids, underwent protodeboronation under basic conditions, presumably due to the more enhanced electron density on the arene ring after the deprotonation of the acidic proton (entries 3 and 4).

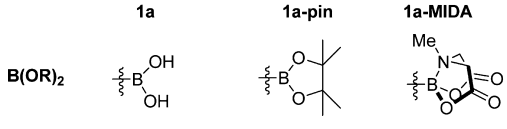
Since several electron-rich arene boronic acids, particularly aniline boronic acid **1a**, turned out to be unstable and readily undergo protodeboronation, we attmepted to develop methods for the synthesisof a stable surrogate for boronic acid **1a** (Scheme 3).[14] The pinacol boronate **1a-pin** could be readily prepared by a simple condensation between **1a** and pinacol under ambient conditions (eq 1). In addition, since we recently demonstrated that the *N*-methyliminodiaectic acid (MIDA) boronates[15,16] of *ortho*- and *para*-phenol boronic acids are benchtop stable surrogates for these unstable boronic acids,[17] we further attempted to prepare MIDA boronate **1a-MIDA** as a stable surrogate for **1a**. When **1a** was subjected to the conditions[15] developed by Burke and co-workers, MIDA boronate **1a-MIDA** was obtained in low yield along with a significant amount of the protodeboronation product **2a** (eq 2). However, when boronic acid **1a** was subjected to the protocol for the synthesis of MIDA boronates for *para*-phenol boronic acids recently developed by our group,[17] delightfully, **1a-MIDA** was obtained in excellent yield without any protodeboronation (eq 3).

With these boronates in hand, the stabilities of the resulting boronates **1a-pin** and **1a-MIDA** were compared with that of their parent boronic acid **1a** (Scheme 4). Both boronates are

Scheme 4. Comparison of Stability of Boronates 1a-pin and 1a-MIDA with 1a



compound	time	yield (%)
1a	2 h	100
1a-pin	4 days	100
1a-MIDA	7 days	100

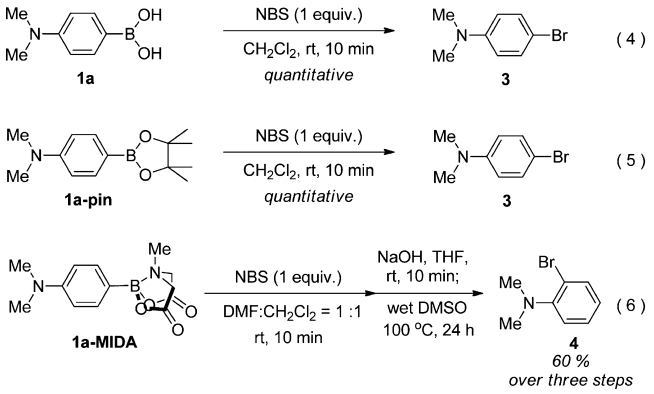


benchtop stable and display enhanced stability even at elevated temperature in DMSO compared to their parent boronic acid; **1a** completely underwent protodeboronation at 100 °C within a couple of hours, whereas **1a-pin** and **1a-MIDA** displayed much higher stability under the same conditions and required 4 and 7 days to complete protodeboronation, respectively.

dx.doi.org/10.1021/jo500780b | J. Org. Chem. 2014, 79, 7277−7285

Since we already demonstrated that the boronic acid moiety could be utilized as a blocking group in EAS reactions with *para*-phenol boronic acid leading to the *ortho*-functionalized phenol, we attempted to extend this strategy to the *ortho*-functionalization of other electron-rich arenes (Scheme 5).

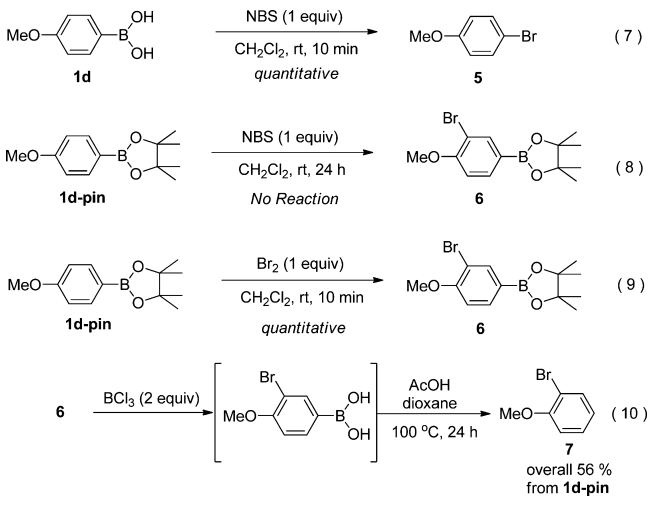
Scheme 5. *ortho*-Bromination of Anilines Using a Boronic Acid Moiety as a Blocking Group



When aniline boronic acid **1a** was treated with *N*-bromosuccinimide (NBS), bromodeboronation exclusively took place to afford 4-bromoaniline **3** in quantitative yield (eq 4).[18] Since we found that the attenuation of Lewis acidity on the boron atom in a boronic acid moiety decreased the rate of bromodeboronation during our previous studies for *ortho*-bromination of phenols,[7] we decided to use the corresponding pinacol boronate **1a-pin** in place of the parent boronic acid **1a** with NBS. However, even with the pinacol boronate **1a-pin**, the bromodeboronation still took place to provide 4-bromoaniline **3** (eq 5). When a less Lewis acidic MIDA boronate **1a-MIDA** was subjected to the bromination reaction with NBS, to our delight, the *ortho*-brominated product **4** was obtained in good yield after the removal of the boronic acid moiety via protodeboronation (eq 6).[19]

With this successful application of the protodeboronation to the synthesis of *ortho*-bromoaniline derivatives, we further extended this strategy to the preparation of *ortho*-brominated anisole derivatives (Scheme 6).[20] Anisole boronic acid **1d** itself

Scheme 6. *ortho*-Bromination of Anisoles Using a Boronic Acid Moiety as a Blocking Group

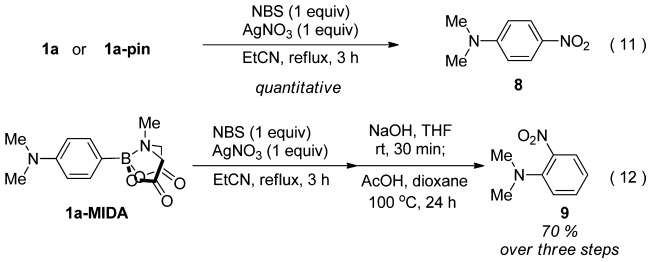


underwent the bromodeboronation reaction with NBS to afford 4-bromoanisole **5** in quantitative yield (eq 7).[21] Since the pinacol boronate turned out to decrease the rate of bromodeboronation compared with the parent boronic acid in our previous studies,[7] we utilized pinacol boronate **1d-pin** in the bromination. However, **1d-pin** displayed much lower reactivity than expected. No bromination reaction took place with NBS, and **1d-pin** remained intact after 24 h (eq 8). When bromine was utilized in place of NBS in the bromination reaction, however, the bromination smoothly took place at the *ortho*-position to the methoxy group to afford compound **6** (eq 9). Rather unexpectedly, the direct removal of the pinacol boronate moiety in compound **6** via protodeboronation turned out to be challenging; the pinacol boronate **6** did not undergo any protodeboronation with either acetic acid or stronger TFA as a proton source. After the pinacol boronate was converted into the corresponding boronic acid with BCl_3, delightfully, protodeboronation smoothly took place to afford the *ortho*-bromoanisole **7** in 56% yield over three steps (eq 10).

With these successful results for the *ortho*-functionalization of anisole and aniline derivatives using a boronic acid as a blocking group, we further attempted to extend this strategy to the *ortho*-bromination of anilide derivatives. However, the boronic acid moiety in anilide boronic acid **1j** did not act as a blocking group as effectively as the ones in aniline and anisole boronic acids **1a** and **1d**; boronic acid **1j** and its pinacol boronate **1j-pin** underwent bromodeboronation reaction. Rather disappointingly, even with MIDA boronate **1j-MIDA**, bromodeboronation still took place and a rather complex mixture was obtained.

With successful application of a boronic acid moiety as a blocking group in the bromination reaction, we further attempted to extend this strategy to other EAS reactions, such as nitration, with electron-rich arene boronic acids (Scheme 7).[22] When aniline boronic acid **1a** and its pinacol

Scheme 7. *ortho*-Nitration of Anilines Using a Boronic Acid Moiety as a Blocking Group

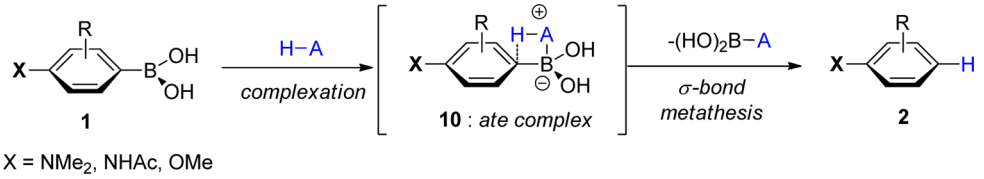


boronate **1a-pin** were subjected to the nitration conditions, the nitration took place predominately at the *ipso*-position to the boronic acid moiety, yielding 4-nitroaniline **8** (eq 11).[23] With MIDA boronate **1a-MIDA**, however, the MIDA boronate moiety successfully worked as a blocking group under nitration conditions, and the corresponding *ortho*-nitroaniline **9** was obtained in good yield after the removal of the boronic acid moiety via protodeboronation (eq 12).[24]

With these results in hand, several control experiments were carried out to gain information to elucidate the reaction mechanism for this protodeboronation of electron-rich arene boronic acids. Similar to the proposed reaction mechanism for the protodeboronation of *para*-phenol boronic acids,[7] we hypothesized that the protodeboronation of these electron-rich arene boronic acids might proceed via a two-step sequence:

dx.doi.org/10.1021/jo500780b | J. Org. Chem. 2014, 79, 7277−7285

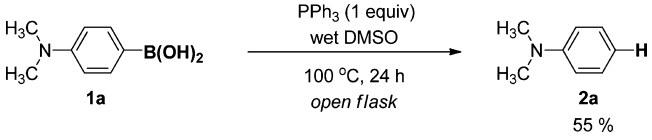
Scheme 8. Proposed Reaction Mechanism for Protodeboronation



complexation of a protic acid with the boron atom to form ate complex **10** and subsequent σ-bond metathesis (Scheme 8).

In order to test this proposed reaction mechanism, we first investigated the importance of the complexation of the boron with a protic acid to form ate complex **10** on the protodeboronation. As demonstrated in Scheme 4, the Lewis acidity of the boron atom had a strong influence on the protodeboronation; as the Lewis acidity on the boron decreased, a boronic acid was more reluctant to form a complex with a proton source, leading to slow protodeboronation. To further prove the importance of the formation of complexation on this protodeboronation, the reaction was performed in the presence of a Lewis basic ligand, which could compete with a proton source in the complex formation. For instance, when the reaction was carried out in the presence of PPh_3, the protodeboronation significantly slowed down and the corresponding aniline **2a** was obtained in only 55% even after 24 h (Scheme 9).[25]

Scheme 9. Protodeboronation of 1a in the Presence of Lewis Basic PPh_3



Next, the effect of an external protic acid on this thermal protodeboronation was examined. During the investigation of reaction parameters, it was found that the presence of external proton sources, such as water, exhibited a significant effect on the protodeboronation of **1a**. For example, protodeboronation of **1a** was completed in wet DMSO within 2 h at 100 °C, whereas, in the presence of molecular sieves, **1a** required 48 h to undergo complete protodeboronation (Table 1, entries 1 and 8). In addition, the acidity of an external protic acid showed the proportional relationship with the reactivity of protodeboronation of **1a** (Table 2); the rate of protodeboronation of **1a** increased with the acidity of an external proton source. These results might be because a more acidic proton source facilitates σ-bond metathesis from the ate complex **10** to afford the corresponding arenes **2** and a boric acid derivative.

In addition to the acidity of an external proton source, the electron density of the arene ring system in the boronic acid facilitated the protodeboronation (see Scheme 2). For example, highly electron-rich aniline boronic acid **1a** smoothly underwent protodeboronation even with water (pK_a = 16), whereas moderately electron-rich anisole and anilide boronic acids **1d** and **1f** did not undergo protodeboronation with water and required acetic acid (pK_a = 4.7) to promote the protodeboronation, and no protodeboronation of alkyl-substituted phenyl boronic acids, such as **1b** and **1c**, was observed even with much stronger TFA (pK_a = −0.25). Along this line, the enhanced reactivity of anilide boronic acid **1j** under basic conditions might be due to the increased electron density of the arene ring after the removal of a proton under basic conditions.[26] These results strongly suggested that the electron density of the arene ring system in the boronic acid significantly increases the reactivity in the protodeboronation due to the facilitation of σ-bond metathesis from the ate complex. On the basis of these results, we believed that the protodeboronation reaction would proceed via the proposed mechanism shown in Scheme 8.

CONCLUSION

We described the metal-free thermal protodeboronation of various electron-rich arene boronic acids. Investigating the controlling reaction parameters, such as solvent, temperature, and a proton source, we provided suitable reaction conditions for the protodeboronation of several types of electron-rich arene boronic acids carrying a different substituent at the *para*-position to the boronic acid. Furthermore, a protocol for the *ortho*-functionalization of electron-rich arenes was developed using the boronic acid moiety as a blocking group in EAS reactions and subsequent carbon−boron bond cleavage in the boronic acid moiety via this thermal protodeboronation. This protodeboronation is believed to proceed through the coordination of a proton source to the boron atom on the boronic acid, followed by σ-bond metathesis, to afford the corresponding arene compounds. Further applications of these thermal protodeboronations of electron-rich arene boronic acids are currently underway in our laboratory.

EXPERIMENTAL SECTION

General. All reactions were carried out in oven-dried glassware under an air 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 phosphomolybdic acid solution as an indicator. Flash column chromatography was performed according to the method of Still[27] using silica gel 60 (230−400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. All boronic acids were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded on 300 and 400 MHz spectrometers and ^{13}C NMR spectra were recorded on 75 and 100 MHz spectrometers, respectively. Tetramethylsilane and $CDCl_3$ were used as internal standards for ^{1}H NMR (δ: 0.0 ppm) and ^{13}C NMR (δ: 77.16 ppm), respectively. The proton spectra were reported as follows: δ (position of proton, multiplicity, coupling constant J, number of protons) and the carbon spectra were reported only δ (position of carbon). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (heptet), m (multiplet), and br (broad). High-resolution mass spectra (HRMS) were obtained using a quadrupole instrument using electron ionization (EI) as the ionization method.

General Procedure for Thermal Protodeboronation of Electron-Rich Arene Boronic Acids 1 (Scheme 2). Method A: A solution of arene boronic acid **1** (0.10 mmol; 1.0 equiv) in wet DMSO (2.0 mL) was heated to 100 °C in an open flask, and the reaction mixture was monitored by TLC. On the complete

dx.doi.org/10.1021/jo500780b | J. Org. Chem. 2014, 79, 7277−7285

consumption of **1**, the reaction mixture was cooled to room temperature and concentrated. The crude mixture was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes (EtOAc:hexanes = 1:20) as an eluent.

Method B: A solution of arene boronic acid **1** (0.50 mmol; 1.0 equiv) and AcOH (0.050 mL; 2.5 mmol; 5.0 equiv) in 1,4-dioxane (10 mL) was allowed to stir at 100 °C in an open flask, and the reaction mixture was monitored by TLC. Once **1** was completely consumed, the reaction mixture was cooled to room temperature and concentrated. The crude mixture was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes (EtOAc:hexanes = 1:20) as an eluent.

Method C: To a solution of arene boronic acid **1** (0.10 mmol; 1.0 equiv) in DMSO (1.0 mL) was added K_2CO_3 (0.069 g; 0.50 mmol; 5.0 equiv). The reaction mixture was heated 100 °C in an open flask and monitored by TLC. On the complete consumption of **1**, the reaction mixture was cooled to room temperature. The crude mixture was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes (EtOAc:hexanes = 1:20) as an eluent.

*N,N-Dimethylaniline (**2a**).* Compound **2a** was obtained as a colorless liquid. The spectroscopic data of **2a** obtained were in good agreement with the literature.[28] Yield: 0.011 g (94%, Method A); 0.056 g (93%, Method B). ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm) δ 7.25 (t, J = 7.8 Hz, 2H), 6.76−6.70 (m, 3H), 2.94 (s, 6H).

*Anisole (**2d**).* Compound **2d** was obtained as a colorless liquid. The spectroscopic data of **2d** obtained were in good agreement with a commercially available sample.[29] Yield: 0.050 g (92%, Method B). ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm) δ 7.32−7.27 (m, 2H), 6.98−6.90 (m, 3H), 3.81 (s, 3H).

Boronic acid **1f** also provided anisole **2d** in 93% yield (0.050 g, Method B).

*1,3-Dimethoxybenzene (**2g**).* Compound **2g** was obtained as a white solid. The spectroscopic data of **2g** obtained were in good agreement with the literature.[30] Yield: 0.064 g (93%, Method B). ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm) δ 7.20 (t, J = 8.2 Hz, 1H), 6.54−6.48 (m, 3H), 3.81 (s, 6H).

Boronic acid **1h** also provided anisole **2g** in 91% yield (0.063 g, Method B).

*1,2-Dimethoxybenzene (**2i**).* Compound **2i** was obtained as a white solid. The spectroscopic data of **2i** obtained were in good agreement with the literature.[31] Yield: 0.067 g (97%, Method B). ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm) δ 6.96−6.88 (m, 4H), 3.90 (s, 6H).

*N-Phenylacetamide (**2j**).* Compound **2j** was obtained as a white solid. The spectroscopic data of **2j** obtained were in good agreement with the literature.[32] Yield: 0.065 g (96%, Method B); 0.013 g (96%, Method C). ^{1}H NMR (300 MHz, DMSO, 2.5 ppm) δ 9.91 (s, 1H), 7.55 (d, J = 7.7 Hz, 2H), 7.27 (t, J = 7.9 Hz, 2H), 7.00 (t, J = 7.6 Hz, 1H), 2.02 (s, 3H).

Synthesis of Stable Surrogates 1a-pin and 1a-MIDA for Boronic Acid 1a. *Synthesis of **1a-pin**.* To a round-bottom flask were added **1a** (0.17 g; 1.0 mmol; 1.0 equiv) and pinacol (0.12 g; 1.0 mmol; 1.0 equiv) and toluene (10 mL). The reaction mixture was stirred under an argon atmosphere at room temperature and monitored by TLC. On the complete consumption of **1a**, the reaction mixture was extracted with EtOAc. The organic layer was combined, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexanes (EtOAc:hexanes = 1:5) to afford compound **1a-pin** as a colorless oil. The spectroscopic data were in good agreement with the literature.[33] Yield: 0.22 g (89%). ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm) δ 7.68 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 2.98 (s, 6H), 1.32 (s, 12H).

*Synthesis of **1a-MIDA**.* A mixture of **1a** (0.17 g; 1.0 mmol; 1.0 equiv) and MIDA (0.44 g; 3.0 mmol; 3.0 equiv) and molecular sieves (0.36 g) was dissolved in DMF (10 mL). The reaction mixture was heated at 120 °C under an argon atmosphere and monitored by TLC. On the complete formation of MIDA boronate from **1a**, the reaction mixture was cooled to room temperature and concentrated. The crude mixture was redissolved in acetone. The resulting MIDA boronate is soluble in acetone, whereas a reacting MIDA is not soluble in that solvent. The undissolved solid was collected by filtration to recover MIDA. The filtrate was purified by flash column chromatography on silica gel using acetone as an eluent to afford a white solid. Then, the solid obtained was redissolved in a minimum of acetone to which Et_2O was slowly added to promote crystallization. MIDA boronate **1a-MIDA** was collected by filtration as a white solid. Yield: 0.25 g (90%). ^{1}H NMR (300 MHz, DMSO-d_6, 2.50 ppm) δ 7.21 (d, J = 9.5 Hz, 2H), 6.69 (d, J = 8.5 Hz, 2H), 4.26 (d, J = 17.3 Hz, 2H), 4.02 (d, J = 17 Hz, 2H), 2.89 (s, 6H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ 172.3, 170.2, 151.46, 133.9, 112.3, 62.1, 57.4, 48.0. HRMS (EI) calcd for $C_{13}H_{17}BN_2O_4$ 276.1281, found 276.1281.

***ortho*-Functionalization of Electron-Rich Arene Boronic Acids Using a Boronic Acid Moiety as a Blocking Group in EAS Reactions.** *Synthesis of 2-Bromo-N,N-dimethylaniline (**4**).* A solution of MIDA boronate **1a-MIDA** (0.28 g; 1.0 mmol; 1.0 equiv) and *N*-bromosuccinimide (NBS, 0.21 g; 1.2 mmol; 1.2 equiv) in a mixture of DMF and CH_2Cl_2 (1:1, 10 mL) was allowed to stir under an argon atmosphere at room temperature, and the reaction was monitored by TLC. On the complete consumption of **1a-MIDA**, the reaction mixture was concentrated under reduced pressure. The crude mixture was redissolved in THF (10 mL), and 1.0 M NaOH (3.0 mL; 3.0 mmol; 3.0 equiv) was added to the solution. The resulting mixture was stirred at room temperature and monitored by TLC. After complete consumption of the resulting MIDA boronate, a saturated aqueous solution of ammonium chloride (9.0 mL) was added, and then the reaction was stirred vigorously for 5 min. The resulting mixture was poured into a 100 mL separatory funnel and extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was dissolved in 1,4-dioxane (10 mL) and AcOH (0.30 mL). The reaction mixture was stirred at 100 °C and monitored by TLC. After complete protodeboronation of the resulting boronic acid, the reaction mixture was cooled to room temperature and concentrated. The crude residue was further purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexanes (EtOAc:hexanes = 1:15) to afford the compound as a light yellow oil. Yield: 0.12 g (60%) over three steps. The spectroscopic data were in good agreement with the literature.[19] ^{1}H NMR (300 MHz, $CDCl_3$, 7.26 ppm) δ 7.57−7.54 (m, 1H), 7.29−7.24 (m, 1H), 7.11−7.08 (m, 1H), 6.92−6.87 (m, 1H), 2.80 (s, 6H).

*Synthesis of 2-Bromoanisole (**7**).* To a solution of **1d-pin** (0.23 g; 1.0 mmol, 1.0 equiv) in CH_2Cl_2 was added a solution of bromine (0.050 mL; 1.1 mmol; 1.1 equiv) in CH_2Cl_2 (10 mL) under an argon atmosphere. The resulting mixture was stirred at room temperature and monitored by TLC. On the complete consumption of **1d-pin**, the reaction mixture was concentrated under reduced pressure. The crude mixture was redissolved in CH_2Cl_2 (10 mL), and 1.0 M BCl_3 in CH_2Cl_2 (2.0 mL; 2.0 mmol; 2.0 equiv) was added to the above solution. The resulting mixture was stirred at room temperature for 30 min. After complete hydrolysis of the pinacol boronate, the reaction mixture was concentrated under reduced pressure. To the crude residue redissolved in 1,4-dioxane (10 mL) was added AcOH (0.30 mL), and the reaction mixture was stirred at 100 °C. After complete consumption of the resulting boronic acid, the reaction mixture was cooled to room temperature and concentrated. The crude residue was further purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexanes (EtOAc:hexanes = 1:15) to afford the compound as a light yellow oil. Yield: 0.10 g (55%) over three steps. The spectroscopic data were in good agreement with the literature.[34] ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.56−7.53 (m, 1H), 7.31−7.26 (m, 1H), 6.92−6.81 (m, 2H), 3.90 (s, 3H).

*Synthesis of 2-Nitro-N,N-dimethylaniline (**9**).* To a round-bottom flask were added MIDA boronate **1a-MIDA** (0.055 g; 0.20 mmol; 1.0 equiv), *N*-bromosuccinimide (NBS, 0.036 g; 0.20 mmol; 1.0 equiv), and silver nitrate ($AgNO_3$, 0.034 g; 0.20 mmol; 1.0 equiv). The flask was sealed with a septum and charged under argon, and to it was added EtCN (4 mL). The reaction mixture was stirred at reflux and monitored by TLC. On the complete consumption of **1a-MIDA**, the reaction mixture was concentrated, and the crude mixture was directly subjected to column chromatography over silica gel using EtOAc

dx.doi.org/10.1021/jo500780b | J. Org. Chem. 2014, 79, 7277−7285

without further workup. The isolated product was dissolved in THF (6.0 mL), and to it was added 1.0 M NaOH (0.60 mL; 0.60 mmol; 3.0 equiv). The resulting mixture was stirred at room temperature and monitored by TLC. After complete conversion of the MIDA boronate into the corresponding boronic acid, a saturated aqueous solution of ammonium chloride (1.8 mL) was added to the above solution, and then the reaction mixture was vigorously stirred for 5 min. The resulting mixture was poured into a 25 mL separatory funnel and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated. The crude residue was redissolved in 1,4-dioxane (4.0 mL), and to it was added AcOH (0.060 mL). The reaction mixture was stirred at 100 °C until the protodeboronation was completed. After complete protodeboronation, the reaction mixture was cooled to room temperature and concentrated. The crude residue was further purified by flash chromatography on silica gel (EtOAc:hexanes = 1:15) to afford the desired compound as a light yellow oil. Yield: 0.023 g (70%) over three steps. The spectroscopic data were in good agreement with the literature.[22] ^{1}H NMR (300 MHz, acetone-d_6, 2.05 ppm) δ 7.57−7.54 (d, 1H), 7.32 (t, J = 8.5 Hz, 1H), 7.17 (d, J = 8 Hz, 1H), 6.92 (t, J = 7.7 Hz, 1H), 2.75 (s, 6H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all protodeboronation products **2**, stable surrogates (**1a-pin** and **1a-MIDA**), and *ortho*-functionalized electron-rich arenes (**4**, **7**, and **9**). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +82-2-3290-3147. Fax: +82-2-3290-3121. E-mail: cheon@korea.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (2013R1A1A1008434). C.-H.C. is thankful for the financial support from NRF funded by the Ministry of Education (NRF20100020209). S.-J.A. also thanks Ms. Yoon Bong Oh for the initial investigation of *ortho*-bromination of anisole boronic acid.

■ REFERENCES

(1) Hall, D. G. In *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 1, pp 1−133.

(2) Based on a SciFinder substructure search using phenyl boronic acid, more than 9000 phenyl boronic acid derivatives are commercially available as of April 2014.

(3) Some heteroaromatic boronic acids are generally known to be unstable; see: Tyrrell, E.; Brookes, P. *Synthesis* **2003**, 469−483.

(4) For the previous reports on the protodeboronation of arene boronic acids, see: (a) Kuivila, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2164−2166. (b) Beckett, M. A.; Gilmore, R. J.; Idrees, K. *J. Organomet. Chem.* **1993**, *455*, 47−49. (c) Klingensmith, L. M.; Bio, M. M.; Moniz, G. A. *Tetrahedron Lett.* **2007**, *48*, 8242−8245.

(5) Highly unstable heteroaromatic boronic acids, such as 2-pyridineboronic acid, are known to undergo decomposition via protodeboronation; see: Dick, G. R.; Knapp, D. M.; Gillis, E. P.; Burke, M. D. *Org. Lett.* **2010**, *12*, 2314−2317.

(6) The protodeboronation of allylic and/or alkyl boronic esters has been utilized in stereoselective synthetic methods; see: (a) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096−17098. (b) Elford, T. G.; Nave, S.; Sonawane, R. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16798−16801. (c) Hesse, M. J.; Butts, C. P.; Willis, C. L.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12444−12448.

(7) Lee, C.-Y.; Ahn, S.-J.; Cheon, C.-H. *J. Org. Chem.* **2013**, *78*, 12154−12160.

(8) Highly electron-rich arene boronic acids, such as *para*-phenol and aniline boronic acids, are not benchtop stable and slowly decompose to the corresponding arene compounds at room temperature. However, anisole boronic acid and anilide boronic acid derivatives, bearing a moderately electron-donating substituent on the arene rings, are relatively stable under ambient conditions.

(9) The sulfonyl group has been used as a *para*-blocking group in EAS reactions; see: March, J. In *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; Wiley-VCH: New York, 1992; Chapter 11, p 556.

(10) Recently, our group developed a new method for the synthesis of *ortho*-functionalized phenols using this metal-free protodeboronation where a boronic acid functionality was utilized as a blocking group; see ref 7.

(11) The pK_a values of the proton sources in Table 2 are obtained from the Evans group homepage at Harvard University; see: http://www2.lsdiv.harvard.edu/labs/evans/pdf/evans_pKa_table.pdf.

(12) Ding, F.; Smith, J. M.; Wang, H. *J. Org. Chem.* **2009**, *74*, 2679−2691.

(13) The substituent effect on the protodeboronation is in good accordance with that in reactivity in electrophilic aromatic substitution. For a substituent effect on EAS reactions, see: Carey, F. C.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, 5th ed.; Kluwer Academic/Plenum Publishers: New York, 2001; Chapter 3, pp 335−344.

(14) Although anisole boronic acid **1d** and anilide boronic acid **1j** undergo protodeboronation with acetic acid, these boronic acids are relatively benchtop stable. Thus, we focused on the development of surrogates for more unstable boronic acid **1a**. However, the surrogates for anisole and aniline boronic acids can be prepared by the same protocols described in the article without any difficulty.

(15) For a review on MIDA boronates, see: Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17−27.

(16) (a) Dick, G. R.; Woerly, E. M.; Burke, M. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 2667−2672. (b) Dick, G. R.; Knapp, D. M.; Gillis, E. P.; Burke, M. D. *Org. Lett.* **2010**, *12*, 2314−2317. (c) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961−6963.

(17) Ahn, S.-J.; Lee, C.-Y.; Cheon, C.-H. *Adv. Synth. Catal.* **2014**, *356*, 1767−1772.

(18) Guo, M.; Varady, L.; Fokas, D.; Baldino, C.; Yu, L. *Tetrahedron Lett.* **2006**, *47*, 3889−3892.

(19) Conventionally, *ortho*-brominated *N*,*N*-dialkyl aniline derivatives are prepared via the reduction of 1-bromo-2-nitrobenzene to *ortho*-bromoaniline, followed by further alkylation of the amino group. For more recent examples, see: (a) Colobert, F.; Valdivia, V.; Choppin, S.; Leroux, F. R.; Fernández, I.; Álvarez, E.; Khiar, N. *Org. Lett.* **2009**, *11*, 5130−5133. (b) Bonnaventure, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6330−6340.

(20) *ortho*-Brominated anisole **8** is conventionally prepared by *ortho*-bromination of phenol, followed by methylation. For recent examples, see: (a) Subramanian, T.; Dhakshinamoorthy, A.; Pitchumani, K. *Tetrahedron Lett.* **2013**, *54*, 7167−7170. (b) Herzog, W.; Bronner, C.; Löffler, S.; He, B.; Kratzert, D.; Stalke, D.; Hauser, A.; Wenger, O. S. *ChemPhysChem* **2013**, *14*, 1168−1176.

(21) (a) Thiebes, C.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, 141−142. (b) Zhang, G.; Lv, G.; Li, L.; Chen, F.; Cheng, J. *Tetrahedron Lett.* **2011**, *52*, 1993−1995.

(22) Because **1a** is more prone to undergo protodeboronation under acidic conditions, we need to carry out aromatic nitration reactions under neutral conditions. For a recent example, see: Nowrouzi, N.; Mehranpour, A. M.; Bashiri, E.; Shayan, Z. *Tetrahedron Lett.* **2012**, *53*, 4841−4842.

(23) For recent examples of *ipso*-nitration of arylboronic acids, see: (a) Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maiti, D. *Org. Lett.* **2012**, *14*, 1736−1739. (b) Prakash, G. K. S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2004**, *6*, 2205−2207.
(24) Conventionally, *ortho*-nitro-*N*,*N*-dialkyl aniline derivatives are prepared via nucleophilic aromatic substitution of 1-fluoro-2-nitrobenzene with dialkylamine. For a recent example, see: Ren, P.; Vechorkin, O.; Csok, Z.; Salihu, I.; Scopelliti, R.; Hu, X. *Dalton Trans.* **2011**, *40*, 8906−8911.
(25) Although we attempted to observe the formation of ate complex **10** using ^{11}B NMR spectroscopy at the elevated temperature, unfortunately, we did not observed any peak other than those of the starting boronic acid and boric acid in the ^{11}B NMR spectrum, implying that the σ-bond metathesis from **10** might proceed very rapidly during the protodeboronation.
(26) Phenol boronic acids also display similar reactivity enhancement under basic conditions; see ref 7.
(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(28) Wheaton, C. A.; Bow, J.-P. J.; Stradiotto, M. *Organometallics* **2013**, *32*, 6148.
(29) The identity of anisole was confirmed by the comparison of its ^{1}H NMR with references from Aldrich.
(30) Zhang, J.; Liu, J.-F.; Ugrinov, A.; Pillai, A. F. X.; Sun, Z.-M.; Zhao, P. *J. Am. Chem. Soc.* **2013**, *135*, 17270.
(31) Bhadra, S.; Dzik, W. I.; GooBen, L. J. *Synthesis* **2013**, *45*, 2387.
(32) Wang, W.; Cong, Y.; Zhang, L.; Huang, Y.; Wang, X.; Zhang, T. *Tetrahedron Lett.* **2014**, *55*, 124.
(33) Yamamoto, E.; Izumi, K.; Horita, Y.; Ito, H. *J. Am. Chem. Soc.* **2012**, *134*, 19997.
(34) Lee, Y. M.; Moon, M. E.; Vajpayee, V.; Filimonov, V. D.; Chi, K.-W. *Tetrahedron* **2010**, *66*, 7418.