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Synthesis of Benzimidazole-Substituted Arylboronic Acids *via* Aerobic Oxidation of 1,2-Arylenediamines and Formyl-Substituted Aryl MIDA Boronates using Potassium Iodide as a Catalyst

Ye-Sol Lee[a] and Cheol-Hong Cheon[a,*]

[a] Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 136701, Republic of Korea
Fax: (+82)-2-3290-3121; phone: (+82)-2-3290-3147; e-mail: cheon@korea.ac.kr

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Abstract: A highly efficient protocol for the synthesis of benzimidazole-substituted arylboronic acids was developed *via* aerobic oxidative cyclization of 1,2-aryldiamines and formyl-substituted aryl MIDA (*N*-methyliminodiacetic acid) boronates using potassium iodide as a nucleophilic catalyst. Furthermore, a one-pot protocol for the synthesis of benzimidazole-substituted arylboronic acids from 1,2-phenylenediamines and formyl-substituted arylboronic acids was developed without the isolation of any intermediates. The resulting boronic acids were further subjected to Suzuki–Miyaura coupling reactions without isolation, leading to diaryl-substituted benzimidazoles with only one separation step.

Keywords: aerobic oxidative cyclization; benzimidazole-substituted boronic acids; iodides; *N*-methyliminodiacetic acid (MIDA); MIDA boronates; Suzuki–Miyaura coupling reaction

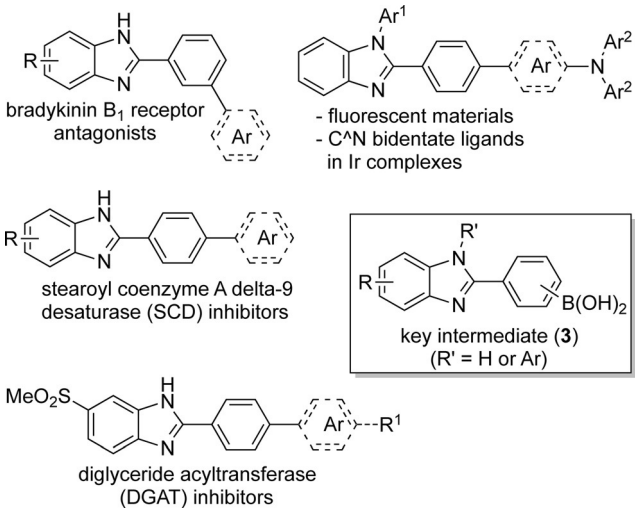
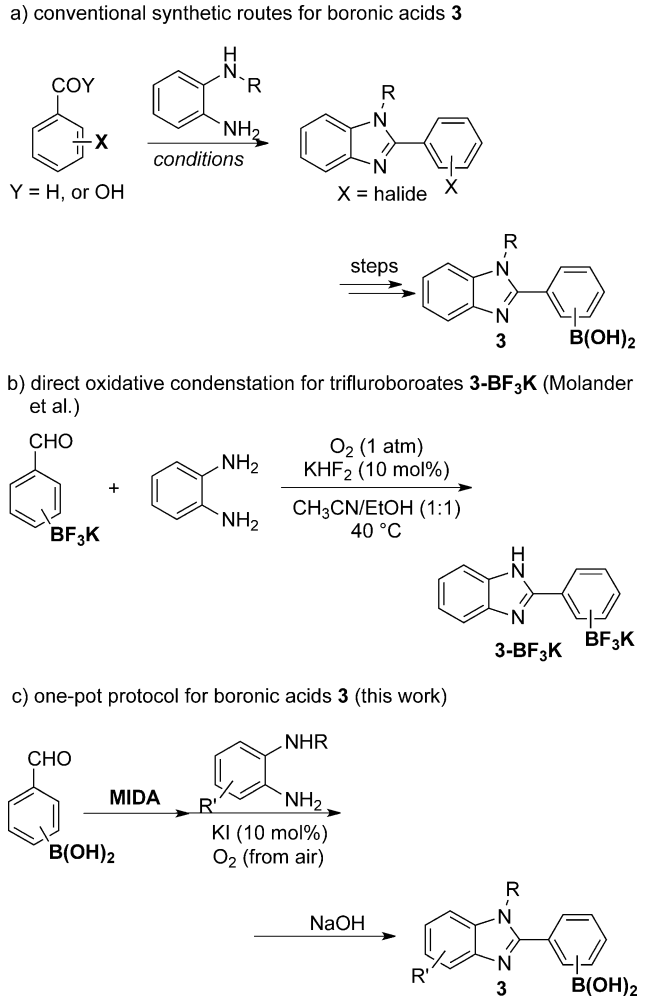


Figure 1. Selected therapeutically active agents and important compounds in materials science that contain 2-arylbenzimidazole moieties. In previous syntheses of these compounds, benzimidazole-substituted arylboronic acids **3** were utilized as key intermediates.[2,3]

Benzimidazole is considered to be an important scaffold that is found in a variety of biologically and therapeutically important natural and pharmaceutical products.[1] For example, various 2-arylbenzimidazoles carrying substituents at either the *meta*- or *para*-position of the aryl group have been extensively investigated as potential candidates for antagonists and/or inhibitors in several pharmaceutical applications.[2] In addition, benzimidazole moieties are frequently used in materials science, particularly in organic light-emitting diodes (OLEDs), as acceptor units in novel push-pull fluorescent materials and/or as precursors for novel monoanionic cyclometalating ligands in iridium complexes (Figure 1).[3]

To maximize positive screening results for libraries of compounds bearing benzimidazole scaffolds and/or fully investigate the structure-property relationship of the resulting materials,[4] it is highly beneficial to be able to rapidly synthesize a variety of benzimidazole derivatives from key intermediates. Among the various intermediates used in the diverse syntheses of derivatives derived from benzimidazoles, benzimidazole-substituted arylboronic acids **3** are often utilized as key intermediates in the reported syntheses of the compounds shown in Figure 1.[2,3]

Conventionally, boronic acids **3** are prepared *via* the subsequent incorporation of a boronic acid functionality from the corresponding halides in pre-generated benzimidazole scaffolds by either electrophilic borylation of trialkyl boronates or metal-catalyzed borylation with a diboron reagent (Scheme 1a).[2,3] However, these methods generally display poor functional group tolerance and often require multi-step synthetic sequences. On the other hand, direct cou-



Scheme 1. (a) Conventional synthetic routes for **3**. (b) Previous example of direct coupling protocol for the synthesis of benzimiazole-substituted trifluoroborates (**3-BF$_3$K**).[5] (c) One-pot protocol for **3** (this work).

pling of 1,2-aryldiamines with an aldehyde carrying a boronic acid functionality is an attractive alternative to conventional methods for the synthesis of **3**. However, there has been only one example of the synthesis of **3** *via* direct oxidative condensation of 1,2-arylenediamines and aldehydes bearing boronic acid functionalities; the Molander group reported the synthesis of benzimidazole-substituted potassium trifluoroborates *via* condensation of 1,2-aryldiamines with formyl-substituted aryltrifluoroborates as boronic acid surrogates under an oxygen atmosphere in the presence of KHF_2 as a catalyst (Scheme 1b).[5]

However, considering the importance and versatility of **3** as intermediates in diverse syntheses of benzimidazole derivatives, we strongly feel that the development of a more general synthetic method for **3** *via* direct oxidative condensation between 1,2-aryldiamines and aldehydes carrying boronic acid functionalities is highly desired. Herein, we report the synthesis of **3** through direct oxidative condensation of 1,2-arylenediamines and formyl-substituted aryl MIDA boronates[6,7,8] under aerobic oxidation conditions using KI as a nucleophilic catalyst[9] (Scheme 1c). A one-pot protocol for the synthesis of **3** was further developed from 1,2-arylenediamines with formylarylboronic acids without isolation of the MIDA boronates. Furthermore, a sequential one-pot protocol for aerobic oxidative cyclization followed by a Suzuki–Miyaura coupling reaction of the resulting MIDA boronates was developed, which allows us to prepare benzimidazole-containing triaromatic products without the isolation of any intermediates.

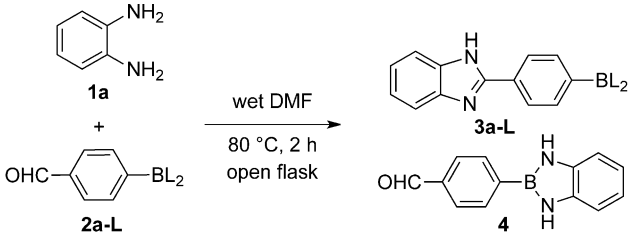
Since the Molander group reported that even trifluoroborate is not completely stable under their oxidative condensation conditions and observed the formation of 2-arylbenzimidazoles *via* protodeboronation of a trifluoroborate moiety,[5] our initial concern was the vulnerability of a boronic acid functionality under oxidative cyclization conditions.[10] In order to overcome the vulnerability of a boronic acid functionality under oxidative cyclization conditions, we needed to develop even milder reaction conditions for this transformation than those[5] developed by the Molander group.

Very recently, our group developed a new protocol for the synthesis of benzimidazoles from 1,2-arylenediamines and aldehydes *via* aerobic oxidative cyclization in wet organic solvents in an open flask without the aid of any metal catalysts/additives.[9] Considering the mildness of those reaction conditions (i.e., no metals, no additives, and in an open flask), we envisaged that this protocol might be applicable to the synthesis of **3** by direct oxidative cyclization from 1,2-aryldiamines with aldehydes bearing boronic acid moieties without any side-reactions, such as protodeboronation of the boronic acid functionality.[10,11]

With this expectation, 1,2-phenylenediamine **1a** and 4-formylphenylboronic acid **2a** were subjected to aerobic oxidation conditions for the synthesis of the benzimidazoles[9] developed by our group (Table 1). However, the expected boronic acid **3a** was not obtained; instead, benzodiazaborole **4** was exclusively formed *via* reaction of **1a** with the boronic acid moiety in **2a** rather than the aldehyde functionality (entry 1). This result implies that the *ortho*-aryldiamine could react with either a boronic acid functionality or an aldehyde functionality, and the reaction of **1a** toward the boronic acid functionality would be faster than that toward the aldehyde functionality.[12] Thus, it was expected that boronic acid **3a** could not be prepared under such conditions without impeding the reaction of **1a** toward the boronic acid functionality in **2a**.

Since a decrease in the Lewis acidity of the boron atom in a boronic acid is generally known to enhance the stability of the boronic acid,[10] the corresponding

Table 1. Reaction of **1a** with **2a** under aerobic oxidative cyclization conditions in wet DMF.



Entry	Aldehyde (**2a-L**)	BL_2	Yield [%][a] **3a-L**	**4**
1	**2a**	$B(OH)_2$	0	100
2	**2a-pin**	B(pin)	0	100
3[b]	**2a-MIDA**	B(MIDA)	60	30

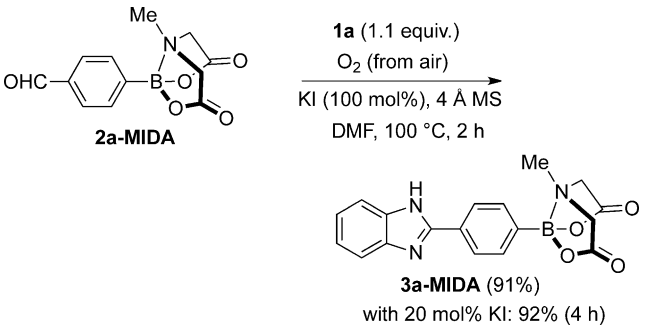
[a] Yields were determined by ^{1}H NMR analysis of the crude mixture using CH_3NO_2 as an internal standard.
[b] Isolated yields of **3a-MIDA** and **4**, respectively.

pinacol boronate **2a-pin** was subjected to the aerobic oxidative cyclization conditions (entry 2). However, even with **2a-pin**, **4** was still exclusively obtained and no formation of benzimidazole **3a-pin** was observed. Rehybridization of the boron center from sp^2 to sp^3 *via* complexation with a ligand is known to further decrease the Lewis acidity of the boron atom, and thus increase the stability of the corresponding boronic acid.[5,7,11] Accordingly, an sp^3-hybridized MIDA (*N*-methyliminodiacetic acid) boronate **2a-MIDA** was tested in this transformation. To our delight, the desired benzimidazole, **3a-MIDA**, was observed in 60% yield along with **4** in a moderate yield (entry 3).

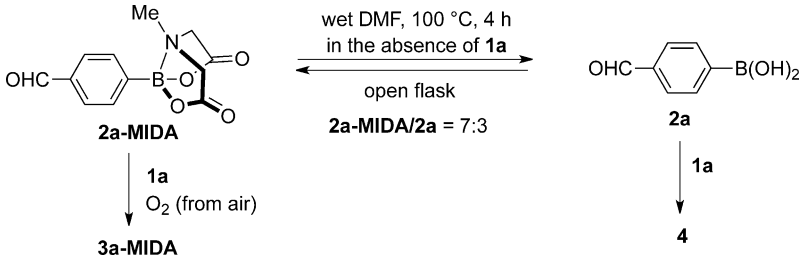
Although **2a-MIDA** provides benzimidazole **3a-MIDA**, the concomitant formation of **4** was rather unexpected because MIDA boronates are generally believed to be stable.[7,11] Thus, we further investigated how **4** was generated from the reaction of **2a-MIDA** with **1a** under aerobic oxidative cyclization conditions in wet DMF. When **2a-MIDA** was subjected to the reaction conditions in wet DMF in the absence of **1a**, surprisingly, **2a-MIDA** underwent partial hydrolysis to generate the parent boronic acid **2a** in a 30% yield (Scheme 2). Under such circumstances, the reaction of **1a** with **2a-MIDA** provides benzimidazole **3a-MIDA**, while the hydrolyzed boronic acid **2a** affords **4** *via* the reaction of **1a** with the boronic acid functionality in **2a**. This result led us to conclude that *the formation of **4** is unavoidable in wet DMF even with MIDA boronates **2**, and a new aerobic oxidative cyclization protocol should be developed under anhydrous conditions.*

During our previous study,[9] we found that iodide could act as an efficient catalyst for the synthesis of benzimidazoles in dry solvents, and developed a novel protocol for the synthesis of benzimidazoles under anhydrous conditions *via* aerobic oxidative cyclization using iodide as a nucleophilic catalyst.[9,13,14] Thus, we decided to explore the possibility of the formation of **3a-MIDA** from **1a** with **2a-MIDA** using KI as a nucleophilic catalyst. When the reaction was performed in the presence of a stoichiometric amount of KI under anhydrous conditions, gratifyingly, aerobic oxidative cyclization smoothly occurred to afford **3a-MIDA** in an excellent yield without the formation of **4**. Furthermore, a catalytic amount of iodide was sufficient to yield **3a-MIDA** without any loss of its efficiency (Scheme 3).

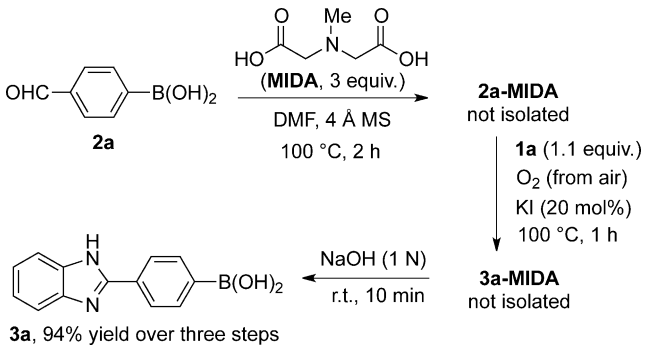
With this result in hand, a one-pot protocol for the synthesis of **3a** from boronic acid **2a** with **1a** was further developed. Here **2a-MIDA**, prepared *in situ* from **2a** and **MIDA** by simple dehydration in the presence of molecular sieves,[15] was subjected to KI-catalyzed aerobic oxidative cyclization with **1a** to generate **3a-MIDA**. Subsequent removal of the MIDA moiety



Scheme 3. Synthesis of **3a-MIDA** *via* aerobic oxidative cyclization using KI as a nucleophilic catalyst



Scheme 2. Rationale for the formation of **4** from **2a-MIDA**.



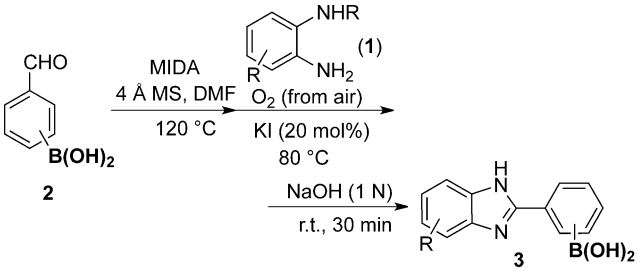
Scheme 4. One-pot protocol for synthesis of **3a** from **2a**.

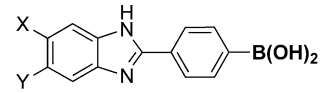
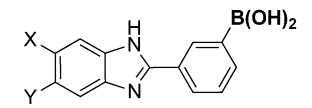
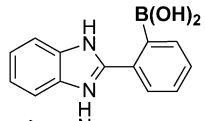
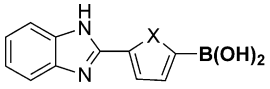
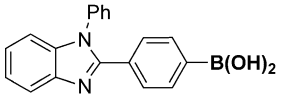
from **3a-MIDA** under aqueous basic conditions[7] afforded the desired boronic acid **3a** in an excellent yield over three steps in the same flask *without isolation of any intermediates* (Scheme 4).

Under these optimized reaction conditions, the substrate scope of this transformation was investigated (Table 2). First, the effect of a substituent on 1,2-phenylenediamines **1** was explored (entries 1–5 and 6–10). Substituents on **1** had little effect on the synthesis of **3**; **1** bearing either electron-donating or electron-withdrawing substituents provided the desired products **3** in excellent yields regardless of the electronic nature of the substituent.[16] Next, the effect of the position of the boronic acid moiety in the aldehydes **2** was investigated (entries 1, 6, and 11). The relative position of the boronic acid moiety to the aldehyde functionality influences this transformation. Benzaldehydes bearing the boronic acid moiety at the *para*- and *meta*-positions provided the corresponding benzimidazoles **3** in high yields (entries 1 and 6), whereas *ortho*-formylphenylboronic acid provided the desired benzimidazole **3k** in a moderate yield (entry 11).[17] *N*-Substituted *ortho*-aryldiamines were also applicable to this protocol. When *N*-phenyl-1,2-phenylenediamine was subjected to the optimized reaction conditions, the corresponding boronic acid **3n** was obtained in an excellent yield (entries 14). Furthermore, this transformation could be performed on a gram scale and the desired boronic acid **3a** was obtained without any loss of efficiency (entry 15). However, the extension of this one-pot protocol to the preparation of benzimidazole-substituted heteroarylboronic acids was not successful (entries 12 and 13). Although the formation of the corresponding boronic acids and the MIDA boronates from formyl-substituted heteroarylboronic acids was observed in the reaction mixture, surprisingly, these boronic acids (**3l** and **3m**) and even the MIDA boronates (**3l-MIDA** and **3m-MIDA**) are unstable, and gradually decomposed during the purification procedure.

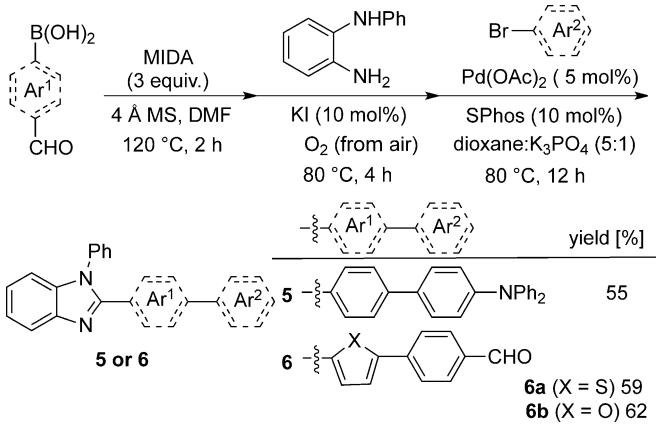
In order to further demonstrate the synthetic utility of this protocol, we attempted to develop a one-pot sequential protocol *via* aerobic oxidative cyclization and cross-coupling reactions leading to benzimidazole-bearing triaromatic products without isolating any intermediates. When **2a-MIDA**, prepared by condensation of **2a** with **MIDA**, was subjected to KI-catalyzed aerobic oxidative cyclization with *N*-phenyl 1,2-phenylenediamine, the corresponding benzimidazole **3n-MIDA** was obtained. Then, **3n-MIDA** was directly subjected to the Suzuki–Miyaura reaction conditions[18] developed by the Burke group without isolation. To our delight, this generated diaryl-substituted benzimidazole **5** in good yield over three steps with only one separation step[19] even though the cross-coupling reaction was not completely optimized (Scheme 5).

Table 2. Substrate scope.



Entry	Product (**3**)		Yield [%][a]
1		**3a** (X = H, Y = H)	94 (93)[b]
2		**3b** (X = Me, Y = H)	91 (70)[b]
3		**3c** (X = Me, Y = Me)	94 (92)[b]
4		**3d** (X = Cl, Y = H)	94 (73)[b]
5		**3e** (X = Cl, Y = Cl)	82 (85)[b]
6		**3f** (X = H, Y = H)	88 (57)[b]
7		**3g** (X = Me, Y = H)	57 (88)[b]
8		**3h** (X = Me, Y = Me)	88 (71)[b]
9		**3i** (X = Cl, Y = H)	75 (78)[b]
10		**3j** (X = Cl, Y = Cl)	84 (86)[b]
11		**3k**	68[c]
12		**3l** (X = S)	-[d] (-)[d]
13		**3m** (X = O)	-[d] (-)[d]
14		**3n**	88 (95)[b]
15[e]		**3a**	96

[a] Isolated yield of **3**.
[b] Numbers in parentheses represent the isolated yields of **3-MIDA**.
[c] Isolated yield after oxidation of the boronic acid moiety in **3k** into a phenolic hydroxy group.
[d] Boronic acids (**3l** and **3m**) and their MIDA boronates are unstable and decomposed during purification.
[e] 10 mmol scale reaction.



Scheme 5. Sequential aerobic oxidative cyclization/cross-coupling reactions of MIDA boronates

This sequential one-pot protocol was further applied to the cross-coupling reactions of benzimidazole-substituted heteroarylboronic acids, which turned out to be unstable, and thus, not able to be isolated in analytically pure forms. When MIDA boronates, prepared *via* aerobic oxidative cyclization of *N*-phenyl-1,2-phenylenediamine and either formyl thienyl or furyl MIDA boronate, were subjected to cross-coupling reaction with aryl bromide, the desired coupling products **6** were obtained in good yields over three steps with only one separation step.

In conclusion, we have developed a highly efficient method for the synthesis of benzimidazole-substituted arylboronic acids through metal-free aerobic oxidative condensation of 1,2-arylenediamines and the MIDA boronate of formylarylboronic acid in the presence of KI as a nucleophilic catalyst. Furthermore, we developed a simple one-pot protocol for the synthesis of benzimidazole-substituted arylboronic acids through the following sequence: MIDA boronate formation, aerobic oxidative cyclization using KI, and subsequent removal of the MIDA moiety. Various types of aromatic aldehydes with boronic acid functionalities were applicable to this protocol, and the desired boronic acids were obtained in high yields. In addition, we successfully demonstrated the utility of this protocol for the direct application of the resulting boronic acids to Suzuki–Miyaura coupling reaction without the isolation of any intermediates.

Experimental Section

General Procedure

To a solution of formyl-substituted arylboronic acid (**2**, 0.50 mmol; 1.0 equiv.) in DMF (4.0 mL) were added *N*-methyliminodiacetic acid (**MIDA**, 1.5 mmol; 3.0 equiv.) and 200 mg of 4 Å molecular sieves. The reaction mixture was allowed to stir at 120 °C under an argon atmosphere, and monitored by TLC. After **2** was completely converted into **2-MIDA**, the reaction mixture was cooled down to room temperature. To the above reaction mixture were added 1,2-aryldiamine (**1**, 0.55 mmol; 1.1 equiv.) and potassium iodide (0.10 mmol, 0.20 equiv.) in one portion. The reaction mixture was exposed to air, and allowed to stir at 80 °C in an open flask until **2-MIDA** was completely consumed. On the complete consumption of **2-MIDA**, the reaction mixture was cooled to room temperature and 3.0 mL of NaOH (1.0 N, 3.0 mmol, 6.0 equiv.) were added to the above reaction mixture. The reaction mixture was stirred at room temperature. After the complete consumption of **3-MIDA**, the reaction mixture was diluted with water (5.0 mL), was extracted with CH_2Cl_2 to remove the remaining 1,2-aryldiamine **1** and other organic impurities. The combined basic aqueous layer was filtered to remove the residual 4 Å molecular sieves. The filtrate was further acidified with 1 N HCl until the pH of the solution became 6–7, where the desired product was precipitated. The precipitate was collected by filtration to provide the desired boronic acid **3**.

For the preparation of 3-MIDA, after the complete consumption of **2-MIDA**, the reaction mixture was concentrated under reduced pressure and the crude product was further purified by solid column chromatography on silica gel to afford the corresponding benzimidazole **3-MIDA**.

Acknowledgements

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[7] For a review on the use of MIDA boronates, see: E. P. Gillis, M. D. Burke, *Aldrichimica Acta* **2009**, *42*, 17.
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[14] For our original demonstration of nucleophile-catalyzed metal-free aerobic oxidative cyclization of imines in the synthesis of benzo-fused azoles, see: Y.-H. Cho, C.-Y. Lee, D.-C. Ha, C.-H. Cheon, *Adv. Synth. Catal.* **2012**, *354*, 2992.
[15] For a detailed procedure of the preparation of MIDA boronates *via* simple condensation in the presence of molecular sieves, see: S.-J. Ahn, C.-Y. Lee, C.-H. Cheon, *Adv. Synth. Catal.* **2014**, *356*, 1767.
[16] The actual yields of both **3** and **3-MIDA** should be higher than the reported values in Table 2. Since some of **3** and **3-MIDA** derivatives displayed poor solubilities, it was difficult to isolate them in analytically pure forms, which often led to lower isolation yields of the desired products.
[17] Due to the high solubility of **3k** in water, we encountered difficulty in isolating **3k** during aqueous work-up. Thus, we determined the yield of **3k** after oxidation of the boronic acid moiety in **3k** into a phenolic hydroxy group.
[18] For the slow-release cross-coupling procedure, see: D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961.
[19] DMF used as the solvent in aerobic oxidation turned out to have a harmful effect on the cross-coupling reaction. Thus, DMF was removed by evaporation prior to the cross-coupling reaction.

