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Aryl Boronic Esters Are Stable on Silica Gel and Reactive under Suzuki–Miyaura Coupling Conditions

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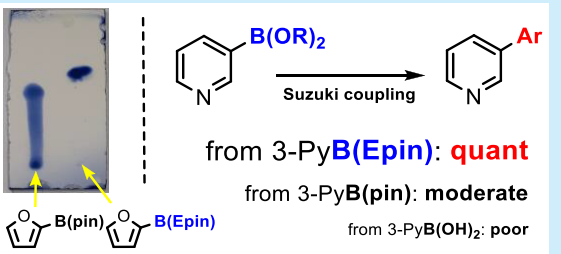
ABSTRACT: A wide range of aryl boronic 1,1,2,2-tetraethylethylene glycol esters [ArB(Epin)s] were readily synthesized. Purifying aryl boronic esters by conventional silica gel chromatography is generally challenging; however, these introduced derivatives are easily purified on silica gel and isolated in excellent yields. We subjected the purified ArB(Epin) to Suzuki–Miyaura couplings, which provided higher yields of the desired biaryl products than those obtained using the corresponding aryl boronic acids or pinacol esters.



Aryl boronic acid derivatives are widely used to synthesize biaryl compounds that are the building blocks of many biologically active compounds, organic materials, and fine chemicals, using Suzuki–Miyaura coupling chemistry.[1,2] However, free aryl boronic acids are associated with several drawbacks. First, the carbon–boron (C–B) bond in an $ArB(OH)_2$ often cleaves during functional group transformations. Second, purifying an $ArB(OH)_2$ using silica gel chromatography is tedious because it strongly absorbs onto silica gel, which leads to lower yields. Third, determining the structure of an $ArB(OH)_2$ is sometimes complicated as it tends to undergo spontaneous partial dehydration to the corresponding boroxine. Consequently, a wide variety of $ArB(OH)_2$ protecting groups have been developed to overcome these challenges.[1,2]

Aryl pinacol boronates, ArB(pin), which are widely used protected aryl boronic acid derivatives, are easily synthesized and directly applicable to Suzuki–Miyaura coupling chemistry. Even though some ArB(pin) derivatives can be purified by silica gel column chromatography, the process should take no more than a few minutes to avoid significant loss of overall yield. Moreover, as is often the case for boronic acid derivatives, purifying an ArB(pin) by silica gel column chromatography is likely to fail. While Isobe et al. developed a new general and highly reproducible method for purifying ArB(pin) derivatives using silica gel treated with boric acid (B-silica gel),[3] the separating power of B-silica gel is much lower than that of normal silica gel; hence, purification is not always successful.

1,8-Diaminonaphthalene aryl boron amides, ArB(dan),[4] and *N*-methyl iminodiacetic aryl boronic anhydrides, ArB(MIDA),[5] were recently reported. These boronic acid derivatives are highly stable under a variety of reaction conditions, including silica gel chromatography, and can be directly used in Suzuki–Miyaura coupling chemistry without deprotection and have been used to successfully synthesize many types of oligoarenes and polyenes. Although ArB(dan) and ArB(MIDA) are broadly useful in industrial and laboratory applications, the direct coupling of ArB(dan) requires strongly alkaline reaction conditions, while the high polarity of ArB(MIDA) hinders purification by silica gel column chromatography.

To overcome the above-mentioned challenges, we developed aryl boronic acid 1,1,2,2-tetraethylethylene glycol esters [ArB(Epin)s] that are easily purified by silica gel chromatography.[6] The four ethyl groups of the boronate are designed to spatially protect the empty orbital of the boron atom in a dynamic manner (Figure 1). We hypothesized that this dynamic protection facilitates the purification of ArB(Epin)s on silica gel and their further use in Suzuki–Miyaura coupling reaction chemistry.

We synthesized ArB(Epin)s **2a–s** using three different methods, as shown in Schemes 1–3. ArB(Epin)s **2a–l** were obtained in good-to-excellent yields through dehydrative esterifications, which involved simply stirring aryl boronic acids **1a–l** with 1,1,2,2-tetraethylethylene glycol (Epin) in CH_2Cl_2 at room temperature (Scheme 1). The reactions of aryl boronic acids bearing electron-donating groups (**1a**, **1c**, **1e**, and **1g**) and electron-withdrawing groups (**1b** and **1f**) produced **2a–c** and **2e–g** in isolated yields of 83–99%. The reactions of sterically hindered 1-naphthalene boronic acid (**1d**) and 2,6-dimethoxyphenyl boronic acid (**1g**) afforded ArB(Epin) **2d** and **2g** in isolated yields of 93–99%, although higher temperatures were required. 1,4-Phenylenediboronic

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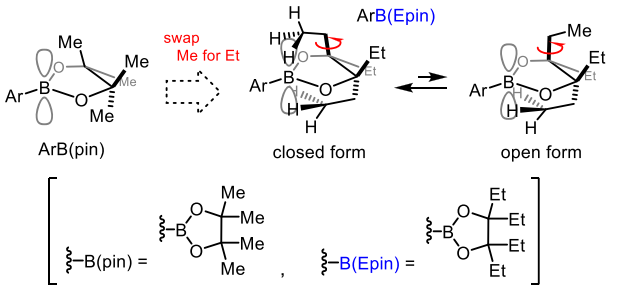
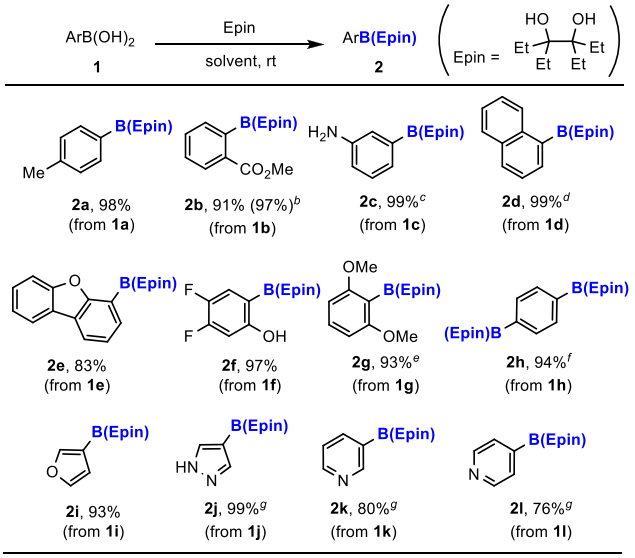


Figure 1. Rationalizing the choice of the B(Epin) group as a new class of aryl boronic ester.

Scheme 1. Synthesis of ArB(Epin)s 2 through the Dehydrative Esterifications of Boronic Acids 1[a]

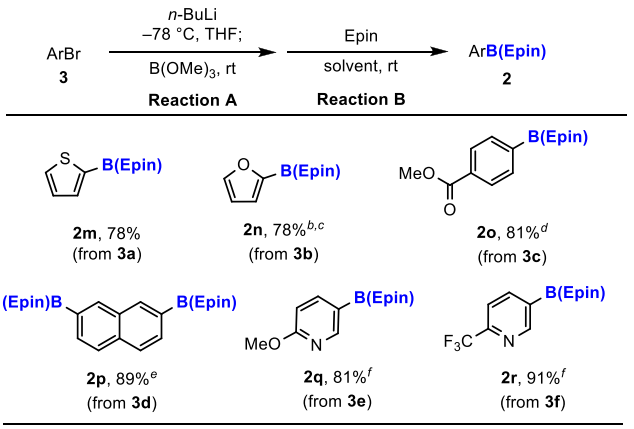


[a]Conditions: $ArB(OH)_2$ **1** (1.0 equiv) and Epin (1.0 equiv) in CH_2Cl_2 (0.10 M) at rt for 16 h. [b]In toluene (0.10 M) at 80 °C for 3 h. [c]$ArB(OH)_2$ **1** (1.1 equiv) in CH_2Cl_2 (0.10 M) at 40 °C for 16 h. [d]In CH_2Cl_2 (0.10 M) at 40 °C for 16 h. [e]In benzene (0.10 M) at 80 °C for 16 h. [f]Epin (2.0 equiv) and reflux in benzene (0.10 M) with a Dean−Stark apparatus for 12 h. [g]AcOH (0.10 equiv) was added in Et_2O (10 μM) at rt.

acid (**1h**) was also double esterified using a Dean−Stark apparatus under reflux conditions. It should be noted that heteroaromatic boronates **2i−l** were obtained in isolated yields of 76−99% by adding 0.10 equiv of AcOH to alkaline heterocycles **1j−l**. We believe that the addition of a catalytic amount of AcOH effectively facilitates the elimination of the hydroxyl group.

ArB(Epin)s **2m−r** were synthesized through the metalative borylation of aryl bromides **3a−f** (Reaction A) followed by esterification (Reaction B) (Scheme 2). 2-Bromothiophene (**3a**), 2-bromofuran (**3b**), 5-bromo-2-methoxypyridine (**3e**), and 5-bromo-2-trifluoromethylpyridine (**3f**) were lithiated using *n*-BuLi followed by borylation and transesterification to afford **2m**, **2n**, **2q**, and **2r** in 78−91% yield. Alkaline heteroaromatic boronates **2q** and **2r** required the addition of AcOH (0.10 equiv) to be effectively synthesized (Reaction B). Importantly, **2n** was obtained only when the acidic workup was omitted following borylation (see Supporting Information for details). The metalation of methoxycarbonyl-functionalized **3c**

Scheme 2. Synthesis of ArB(Epin) 2 through the Metalation of Aryl Bromides 3[a]

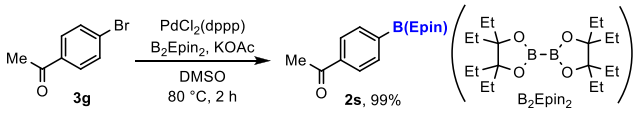


[a]Conditions: ArBr **3** (1.0 equiv), *n*-BuLi (1.2 equiv), $B(OMe)_3$ (2.0 equiv) in THF (0.10 M) for Reaction A. Epin (1.0 equiv) in CH_2Cl_2 for Reaction B. [b]Reaction B at 40 °C. [c]Epin and CH_2Cl_2 were added after evaporating the reaction mixture without quenching. [d]ArBr **3** (1.0 equiv), *i*-PrMgCl·LiCl (1.2 equiv), and $B(OMe)_3$ (2.0 equiv) at −40 °C for Reaction A. [e]ArBr **3** (1.0 equiv), *t*-BuLi (4.2 equiv), and $B(OMe)_3$ (2.4 equiv) for Reaction A. Epin (2.0 equiv) in benzene (0.10 M) at 80 °C for 16 h for Reaction B. [f]ArBr **3** (1.0 equiv) and *n*-BuLi (1.1 equiv) in Et_2O (0.10 M) for Reaction A. Epin (1.0 equiv) and AcOH (0.10 equiv) for Reaction B.

was achieved using *i*-PrMgCl·LiCl at −40 °C.[7] The double lithiation of 2,7-dibromonaphthalene **3d** with *t*-BuLi (4.2 equiv) followed by diborylation afforded **2p** in 89% yield.

ArB(Epin) **2s** was synthesized by palladium-catalyzed Miyaura borylation using bis(1,1,2,2-tetraethylethylene glycolato)diboron (B_2Epin_2, Scheme 3).[8] 4-Bromoacetophenone **3g** was transformed into carbonyl-bearing ArB(Epin) **2s** in an isolated yield of 99% under standard Miyaura borylation conditions using B_2Epin_2 instead of bis(pinacolato)diboron B_2pin_2. It is worth noting that **2s** was completely purified by normal column chromatography on silica gel without any diminution in yield.

Scheme 3. Synthesis of ArB(Epin)s 2 through Miyaura Borylation



We compared the stabilities of ArB(Epin)s **2a**, **2h**, and **2n** on silica gel columns with those of the corresponding ArB(pin)s **2a′**, **2h′**, and **2n′** (Figures 2 and 3). Each pure ArB(Epin) **2** and ArB(pin) **2′** (50 mg each) were loaded onto a silica gel column [silica gel 60N, spherical neutral (40−50 μm), purchased from Kanto Chemical] and eluted with EtOAc (Figure 2). While recovery rates of 22−77% were obtained for **2a′**, **2h′**, and **2n′**, ArB(Epin)s **2a**, **2h**, and **2n** exhibited almost quantitative recovery (98−99%). Among **2a′**, **2h′**, and **2n′**, *p*-tolyl boronate **2a′** was the most stable on silica gel, whereas 2-furyl boronate **2n′** was the least stable. These results reveal that silica gel column chromatography can be used to easily purify **2**. On the other hand, **2′** must be carefully purified using normal silica gel to avoid significantly lower yields.[9,10]

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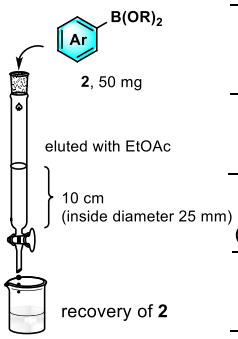


2	recovery of 2	
	B(pin)	B(Epin)
Me, 2a	77% 2a′	99% 2a
(RO)2B, 2h	64% 2h′	98% 2h
2n	22% 2n′	99% 2n

Figure 2. Yields of ArB(Epin)s **2** and ArB(pin)s **2′** obtained by silica gel column chromatography.

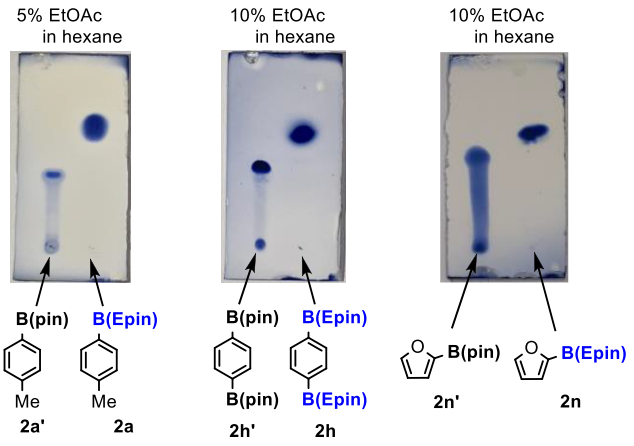
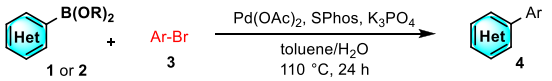


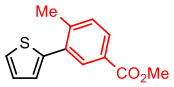
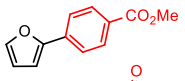
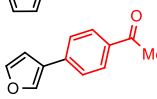
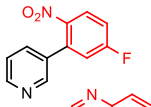
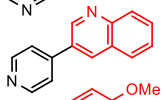
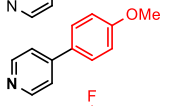
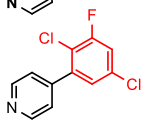
Figure 3. Visualizing the stabilities of ArB(Epin)s **2** by silica gel TLC.

We used a silica gel thin-layer chromatography (TLC) plate [silica gel 60 F_{254}, 0.2 mm plates (Merck)] stained with ceric ammonium molybdate to visualize the silica-gel behavior of ArB(Epin)s **2a**, **2h**, and **2n** and ArB(pin)s **2a′**, **2h′**, and **2n′** (Figure 3). As expected, clear, concentrated, single spots that correspond to **2a**, **2h**, and **2n** were observed at various stages of TLC development, which reveals that these compounds are stable on silica gel. In contrast, **2a′**, **2h′**, and **2n′** exhibited original spots with significant tailing, with **2n′** exhibiting especially strong tailing. These observations are consistent with the silica gel column chromatography results (Figure 2).

To assess the reactivities of ArB(Epin)s **2** and to demonstrate their usefulness for synthesizing heterocyclic biaryl compounds, we subjected them to Suzuki–Miyaura coupling conditions using $Pd(OAc)_2$, SPhos, and K_3PO_4 in toluene/H_2O (Scheme 4, entries 1, 2, 4–6, 8, and 9). We also subjected the corresponding **1** and **2′** to the same reaction conditions for comparison. Notably, the biaryl coupling products **4a–4g** were obtained in the highest yields from ArB(Epin)s **2i** and **2k–2n** in all cases. 2-Thiophenylboronate **2m**, 2- and 3-furanyl boronates **2n** and **2i**, and 3- and 4-pyridinyl boronates **2k** and **2l** were coupled with a wide variety of aryl bromides **3c** and **3g–3l** to afford heterobiaryls **4a–4g** in isolated yields of 73–99%, whereas the corresponding aryl boronic acids **1i**, **1k–1n**, and ArB(pin)s **2i′** and **2k′–2n′** afforded lower product yields (0–73% and 0–95%, respectively).[11] The lower yield of **4m** is possibly attributable to the formation of side products in the presence of SPhos, which can act as a ligand under these reaction conditions, as observed

Scheme 4. Suzuki–Miyaura Coupling Reactions of Heteroaryl Boronic Acids 1 or 2 with Aryl Bromides 3[a]



entry	1, 2	3	product	4	yield (%) B(OH)2	yield (%) B(pin)	yield (%) B(Epin)
1	1m, 2m	3h		4a	73	95	92
2	1n, 2n	3c		4b	5	81	94
3[b]	1n, 2n	3c		4b	0	2	quant
4	1i, 2i	3g		4c	42	93	95
5	1k, 2k	3i		4d	0	53	96
6	1l, 2l	3j		4e	15	58	99
7[c]	1l, 2l	3j		4e	32	47	88
8	1l, 2l	3k		4f	50	69	92
9[d]	1l, 2l	3l		4g	0	0	73

[a]Conditions: ArB$(OR)_2$ **1** or **2** (1.5 equiv), ArBr **3** (1.0 equiv), $Pd(OAc)_2$ (1.0 mol %), SPhos (2.0 mol %), and K_3PO_4 (2.0 equiv) in toluene/H_2O (10:1) at 110 °C for 24 h. [b]Using $Pd(PPh_3)_4$ (1.0 mol %) instead of $Pd(OAc)_2$ and SPhos. [c]Conditions: 4-PyB$(OR)_2$ **1** or **2** (1.5 equiv), ArBr **3** (1.0 equiv), $Pd(PPh_3)_4$ (1.0 mol %), and Cs_2CO_3 (1.5 equiv) in toluene/EtOH (10:1) at 90 °C for 24 h. [d]For 2 h.

during the multiarylation of 1-bromo-2,5-dichloro-3-fluorobenzene (**3l**). The reactions of ArB(Epin) **2n** and **2l** under typical Suzuki–Miyaura coupling conditions with $Pd(PPh_3)_4$ also afforded biaryls **4b** and **4e** in good-to-quantitative yields, while the same products **4b** and **4e** were obtained in lower yields when aryl boronic acids **1n** and **1l** or ArB(pin) **2n′** and **2l′** were used (entries 3 and 7).

To further explore the surprising behavior of these heteroaryl boronic acid derivatives, we subjected 3-PyB(Epin) (**2k**), 3-PyB(pin) (**2k′**), and 3-PyB$(OH)_2$ (**1k**) to stability testing under alkaline conditions in the presence of K_3PO_4 in toluene/H_2O at 110 °C, which, with the exception of the palladium catalyst, are the same reaction conditions used in the Suzuki–Miyaura coupling reaction (Figure 4).[12] We believe that **2k**, **2k′**, and **1k** decompose under aqueous alkaline conditions through their tetracoordinated boronate intermediate **5**. 3-PyB$(OH)_2$ (**1k**) decomposed the fastest, as it disappeared within 12 h, while **2k′** decomposed more slowly, with 17% remaining intact after 12 h. 3-PyB(Epin) (**2k**) proved to be the most stable, as it had not noticeably decomposed even after 24 h under the same conditions, which explains why **2k** yielded the highest relative amount of the Suzuki–Miyaura coupled biaryl product **4d** (Scheme 4, entry 5).

In summary, we developed ArB(Epin)s as stable and easy-to-handle aryl boronates. These aryl boronic acid derivatives are

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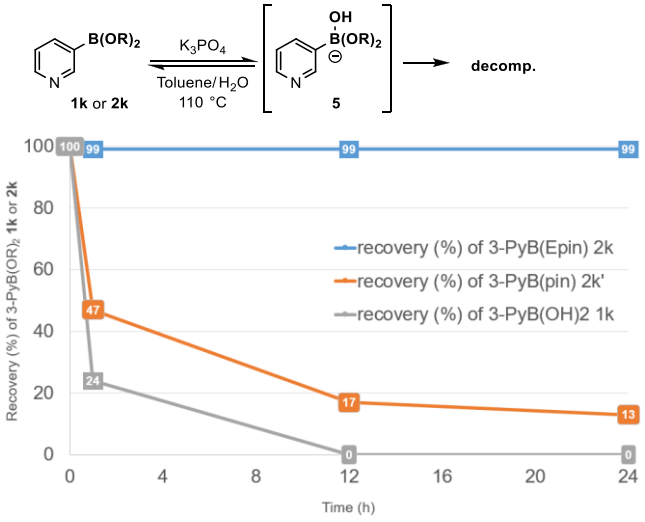

Figure 4. Stabilities of 3-pyridyl boronic acids **1k** or **2k** under alkaline conditions. Conditions: $PyB(OR)_2$ **1k** or **2k** (1.0 equiv) and K_3PO_4 (1.3 equiv) in toluene/H_2O (10:1) at 110 °C.

readily synthesized and purified by column chromatography on silica gel in a manner similar to general organic chemicals. Furthermore, they were directly used to synthesize biaryls using Suzuki−Miyaura coupling chemistry. On the other hand, similar reactions of the corresponding boronic acids or their pinacol esters resulted in lower yields. The detailed features of the ArB(Epin)s and their synthetic applications are currently being explored in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01174.

Detailed experimental procedures, product characterization (NMR, HRMS, etc.), spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews on boronic acid derivatives, see: (a) Hall, D. G., Ed. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Wiley-VCH, 2011. (b) Suzuki, A. Cross-coupling reactions of organoboranes: an easy way to construct C−C bonds (Nobel Lecture). *Angew. Chem., Int. Ed.* **2011**, *50*, 6722−6737. (c) Lennox, A. J. J.; Lloyd-Jones, G. C. Transmetalation in the Suzuki−Miyaura coupling: the fork in the trail. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362−7370. (d) Lennox, A. J. J.; Lloyd-Jones, G. C. Selection of boron reagents for Suzuki−Miyaura coupling. *Chem. Soc. Rev.* **2014**, *43*, 412−443. (e) António, J. P. M.; Russo, R.; Carvalho, C. P.; Cal, P. M. S. D.; Gois, P. M. P. Boronic acids as building blocks for the construction of therapeutically useful bioconjugates. *Chem. Soc. Rev.* **2019**, *48*, 3513−3536. (f) Inglesby, P. A.; Agnew, L. R.; Carter, H. L.; Ring, O. T. Diethanolamine Boronic Esters: Development of a Simple and Standard Process for Boronic Ester Synthesis. *Org. Process Res. Dev.* **2020**, *24*, 1683−1689.

(2) For a selected recent paper of Suzuki−Miyaura couplings, see: (a) Thomas, A. A.; Denmark, S. E. Pre-transmetalation intermediates in the Suzuki-Miyaura reaction revealed: The missing link. *Science* **2016**, *352*, 329−332. (b) Thomas, A. A.; Wang, H.; Zahrt, A. F.; Denmark, S. E. Structural, Kinetic, and Computational Characterization of the Elusive Arylpalladium(II)boronate Complexes in the Suzuki−Miyaura Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 3805−3821. (c) Thomas, A. A.; Zahrt, A. F.; Delaney, C. P.; Denmark, S. E. Elucidating the Role of the Boronic Esters in the Suzuki−Miyaura Reaction: Structural, Kinetic, and Computational Investigations. *J. Am. Chem. Soc.* **2018**, *140*, 4401−4416. (d) Delaney, C. P.; Kassel, V. M.; Denmark, S. E. Potassium Trimethylsilanolate Enables Rapid, Homogeneous Suzuki−Miyaura Cross-Coupling of Boronic Esters. *ACS Catal.* **2020**, *10*, 73−80. (e) Kassel, V. M.; Hanneman, C. M.; Delaney, C. P.; Denmark, S. E. Heteroaryl−Heteroaryl, Suzuki−Miyaura, Anhydrous Cross-Coupling Reactions Enabled by Trimethyl Borate. *J. Am. Chem. Soc.* **2021**, *143*, 13845−13853. (f) Hayes, H. L. D.; Wei, R.; Assante, M.; Geogheghan, K. J.; Jin, N.; Tomasi, S.; Noonan, G.; Leach, A. G.; Lloyd-Jones, G. C. Protodeboronation of (Hetero)Arylboronic Esters: Direct versus Prehydrolytic Pathways and Self-/Auto-Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 14814−14826. (g) Niwa, T.; Uetake, Y.; Isoda, M.; Takimoto, T.; Nakaoka, M.; Hashizume, D.; Sakurai, H.; Hosoya, T. Lewis acid-mediated Suzuki−Miyaura cross-coupling reaction. *Nat. Catal.* **2021**, *4*, 1080−1088.

(3) Hitosugi, S.; Tanimoto, D.; Nakanishi, W.; Isobe, H. A Facile Chromatographic Method for Purification of Pinacol Boronic Esters. *Chem. Lett.* **2012**, *41*, 972−973.

(4) (a) Noguchi, H.; Hojo, K.; Suginome, M. Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki−Miyaura Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 758−759. (b) Noguchi, H.; Shioda, T.; Chou, C. M.; Suginome, M. Differentially Protected Benzenediboronic Acids: Divalent Cross-Coupling Modules for the Efficient Synthesis of Boron-Substituted Oligoarenes. *Org. Lett.* **2008**, *10*, 377−380. (c) Iwadate, N.; Suginome, M. Synthesis of Masked Haloareneboronic Acids via

Iridium-Catalyzed Aromatic C−H Borylation with 1,8-Naphthalenediaminatoborane (danBH). *J. Organomet. Chem.* **2009**, *694*, 1713−1717. (d) Iwadate, N.; Suginome, M. Synthesis of B-Protected β-Styrylboronic Acids via Iridium-Catalyzed Hydroboration of Alkynes with 1,8-Naphthalenediaminatoborane Leading to Iterative Synthesis of Oligo(phenylenevinylene)s. *Org. Lett.* **2009**, *11*, 1899−1902. (e) Iwadate, N.; Suginome, M. Rhodium-Catalyzed Dehydroborylation of Styrenes with Naphthalene-1,8-diaminatoborane [(dan)-BH]: New Synthesis of Masked β-Borylstyrenes as New Phenylene−Vinylene Cross-Coupling Modules. *Chem. Lett.* **2010**, *39*, 558−560. (f) Iwadate, N.; Suginome, M. Differentially Protected Diboron for Regioselective Diboration of Alkynes: Internal-Selective Cross-Coupling of 1-Alkene-1,2-diboronic Acid Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 2548−2549. (g) Mutoh, Y.; Yamamoto, K.; Saito, S. Suzuki−Miyaura Cross-Coupling of 1,8-Diaminonaphthalene (dan)-Protected Arylboronic Acids. *ACS Catal.* **2020**, *10*, 352−357. (h) Yoshida, H.; Seki, M.; Kamio, S.; Tanaka, H.; Izumi, Y.; Li, J.; Osaka, I.; Abe, M.; Andoh, H.; Yajima, T.; Tani, T.; Tsuchimoto, T. Direct Suzuki−Miyaura Coupling with Naphthalene-1,8-diaminato (dan)-Substituted Organoborons. *ACS Catal.* **2020**, *10*, 346−351.

(5) (a) Gillis, E. P.; Burke, M. D. A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki−Miyaura Coupling of B-Protected Haloboronic Acid Building Blocks. *J. Am. Chem. Soc.* **2007**, *129*, 6716−6717. (b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates. *J. Am. Chem. Soc.* **2009**, *131*, 6961−6963. (c) Lennox, A. J. J.; Lloyd-Jones, G. C. The Slow-Release Strategy in Suzuki−Miyaura Coupling. *Isr. J. Chem.* **2010**, *50*, 664−674. (d) Dick, G. R.; Woerly, E. M.; Burke, M. D. A General Solution for the 2-Pyridyl Problem. *Angew. Chem., Int. Ed.* **2012**, *51*, 2667−2672. (e) Li, J.; Grillo, A. S.; Burke, M. D. From Synthesis to Function via Iterative Assembly of *N*-Methyliminodiacetic Acid Boronate Building Blocks. *Acc. Chem. Res.* **2015**, *48*, 2297−2307. (f) Lehmann, J. W.; Blair, D. J.; Burke, M. D. Towards the generalized iterative synthesis of small molecules. *Nat. Rev. Chem.* **2018**, *2*, 0115. (g) Haley, H. M. S.; Hill, A. G.; Greenwood, A. I.; Woerly, E. M.; Rienstra, C. M.; Burke, M. D. Peridinin Is an Exceptionally Potent and Membrane-Embedded Inhibitor of Bilayer Lipid Peroxidation. *J. Am. Chem. Soc.* **2018**, *140*, 15227−15240. (h) Jo, Y.-I.; Burke, M. D.; Cheon, C.-H. Modular Syntheses of Phenanthroindolizidine Natural Products. *Org. Lett.* **2019**, *21*, 4201−4204. (i) Lee, J.; Park, H.; Hwang, S.-H.; Lee, I.-H.; Choi, T.-L. RuPhos Pd Precatalyst and MIDA Boronate as an Effective Combination for the Precision Synthesis of Poly(3-hexylthiophene): Systematic Investigation of the Effects of Boronates, Halides, and Ligands. *Macromol.* **2020**, *53*, 3306−3314. (j) Li, X.; He, C.; Matyjaszewski, K.; Pan, X. ATRP of MIDA Boronate-Containing Monomers as a Tool for Synthesizing Linear Phenolic and Functionalized Polymers. *ACS Macro Lett.* **2021**, *10*, 1327−1332.

(6) For pioneering works on allylic B(Epin), see: (a) Incerti-Pradillos, C. A.; Kabeshov, M. A.; Malkov, A. V. Highly Stereoselective Synthesis of Z-Homoallylic Alcohols by Kinetic Resolution of Racemic Secondary Allyl Boronates. *Angew. Chem., Int. Ed.* **2013**, *52*, 5338−5341. (b) Villar, L.; Orlov, N. V.; Kondratyev, N. S.; Uria, U.; Vicario, J. L.; Malkov, A. V. Kinetic Resolution of Secondary Allyl Boronates and Their Application in the Synthesis of Homoallylic Amines. *Chem. Eur. J.* **2018**, *24*, 16262−16265.

(7) (a) Krasovskiy, A.; Knochel, P. A LiCl-Mediated Br/Mg Exchange Reaction for the Preparation of Functionalized Aryl- and Heteroarylmagnesium Compounds from Organic Bromides. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333−3336. (b) Krasovskiy, A.; Straub, B. F.; Knochel, P. Highly Efficient Reagents for Br/Mg Exchange. *Angew. Chem., Int. Ed.* **2006**, *45*, 159−162. (c) Hauk, D.; Lang, S.; Murso, A. Minimization of Side Reactions in Bromine Magnesium Exchanges with *i*-PrMgCl/LiCl and *s*-BuMgCl/LiCl Mixtures. *Org. Process Res. Dev.* **2006**, *10*, 733−738. (d) Kunz, T.; Knochel, P. Synthesis of Functionalized Benzo[*b*]thiophenes by the Intramolecular Copper-Catalyzed Carbomagnesiation of Alkynyl(aryl)thioethers. *Angew. Chem., Int. Ed.* **2012**, *51*, 1958−1961. (e) Nickel, J.; Fernandez, M.; Klier, L.; Knochel, P. Synthesis of Pyrrolo[2,3-*d*]pyrimidines by Copper-Mediated Carbomagnesiations of *N*-Sulfonyl Ynamides and Application to the Preparation of Rigidin A and a 7-Azaserotonin Derivative. *Chem. Eur. J.* **2016**, *22*, 14397−14400. (f) Ziegler, D. S.; Wei, B.; Knochel, P. Improving the Halogen−Magnesium Exchange by using New Turbo-Grignard Reagents. *Chem. Eur. J.* **2019**, *25*, 2695−2703.

(8) (a) Ishiyama, T.; Murata, M.; Miyaura, N. Palladium(0)-Catalyzed Cross-Coupling Reaction of Alkoxydiboron with Haloarenes: A Direct Procedure for Arylboronic Esters. *J. Org. Chem.* **1995**, *60*, 7508−7510. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447−3450. (c) Kuwano, R.; Lee, E.; Won, S. Economical and Readily Accessible Preparation of *o,o*-Disubstituted Arylboronates through Palladium-Catalyzed Borylation of Haloarenes. *Org. Lett.* **2021**, *23*, 9649−9653. (d) Bose, S. K.; Mao, L.; Kuehn, L.; Radius, U.; Nekvinda, J.; Santos, W. L.; Westcott, S. A.; Steel, P. G.; Marder, T. B. First-Row d-Block Element-Catalyzed Carbon−Boron Bond Formation and Related Processes. *Chem. Rev.* **2021**, *121*, 13238−13341.

(9) The MIDA ester of 2-furan boronic acid **2n″** was quantitatively recovered by the same silica gel column chromatography using MeCN instead of EtOAc as an eluent.

(10) For an example using boronates without isolation, see: Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. Microwave Accelerated Iridium Catalyzed Borylation of Aromatic C−H Bonds. *Org. Lett.* **2009**, *11*, 3586−3589.

(11) The coupling reaction of MIDA ester **2n″** afforded the biaryl compound **4b** in 30% yield under the same reaction conditions, most likely because the corresponding boronic acid **1n** (from **2n″**) is generated too rapidly and decomposes under the reaction conditions. In contrast, reactions of both **2n** and **2n″** provided **4b** in high yields (80% and 78%, respectively) under the conditions optimized for MIDA esters (see Supporting Information).

(12) (a) Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C. Protodeboronation of heteroaromatic, vinyl, and cyclopropyl boronic acids: pH−rate profiles, autocatalysis, and disproportionation. *J. Am. Chem. Soc.* **2016**, *138*, 9145−9157. (b) Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. C. Base-catalyzed aryl-B(OH)$_2$ protodeboronation revisited: from concerted proton transfer to liberation of a transient aryl anion. *J. Am. Chem. Soc.* **2017**, *139*, 13156−13165. (c) Hayes, H. L. D.; Wei, R.; Assante, M.; Geogheghan, K. J.; Jin, N.; Tomasi, S.; Noonan, G.; Leach, A. G.; Lloyd-Jones, G. C. Protodeboronation of (Hetero)Arylboronic Esters: Direct versus Prehydrolytic Pathways and Self-/Auto-Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 14814−14826.

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