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Scyllo-inositol as a convenient protecting group for aryl boronic acids in Suzuki–Miyaura cross-coupling reactions

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ABSTRACT

Herein, we report air- and water-stable borate complexes between *scyllo*-inositol and aryl boronic acids. The complexes were less reactive than free aryl boronic acids under Suzuki–Miyaura cross-coupling reaction conditions; thus, the borate complexes were used as protected boronic acids. Although protecting groups for organoboronic acids are useful in coupling reactions, especially those used to produce π-conjugated molecules, only a few reports describing the use of protecting groups for boronic acids have been published. The proposed unique structural borate complex provides a novel protective method for aryl boronic acids.

Suzuki–Miyaura cross-coupling is an important and versatile reaction in organic synthesis, from the lab to industrial scale, because it permits the formation of C–C bonds under mild conditions.[1] In a typical Suzuki–Miyaura coupling reaction, bi-aryls are formed from the reaction of an aryl boronic acid and an aryl halide in the presence of a base, palladium catalyst, and solvent, which often contains water. Further studies on Suzuki–Miyaura coupling reactions have been expanded in recent decades to include the development of useful ligands for metal complexes[2] and novel reaction conditions.[3] In addition, several studies focused on the evolution of boron functional groups, which are important in the transmetalation step to the metal catalyst in the coupling reaction.[4]

As part of our ongoing research into inositols, we found that *scyllo*-inositol formed an air- and water-stable complex with two mole equivalents of an aryl boronic acid and an alkali metal hydroxide, as described in further detail. Although a double tridentate complex of *scyllo*-inositol and boric acid, $B(OH)_3$, was first reported by Weissbach in 1958[5], complexes between *scyllo*-inositol and aryl boronic acids, $ArB(OH)_2$, have not been studied to the best of our knowledge. Meanwhile, Yamamoto and Miyaura et al. reported that cyclic triolborates between 1,1,1-tris(hydroxymethyl)ethane and organoboronic acids were potent reagents for metal catalyzed C–C and C–N bond forming reactions without base activation.[4d] This Letter motivated us to investigate the reactivity of our *scyllo*-inositol and aryl boronic acid complexes (SABC) in Suzuki–Miyaura cross-coupling reactions. A potassium salt complex of *scyllo*-inositol and 4-methylphenylboronic acid (**1**) poorly reacted with 4-bromobenzoic acid methyl ester, 1-bromo-4-methylbenzene, or 1-bromo-4-methoxybenzene in EtOH/H_2O (5/1) at 50 °C for 5 h (Table 1).[6]

Alternatively, a complex between (1α,3α,5α)-1,3,5-cyclohexanetriol and 4-methylphenylboronic acid (**1a**), which was prepared according to conditions similar to that of SABC for the sake of structural comparison, afforded the coupling compounds in better yields with or without base. Although a cross-coupling reaction between **1a** and 1-bromo-4-methoxybenzene resulted in moderate yield (56%, entry vii), a different reaction condition improved the yield to 79% (entry viii). Thus, considering that cyclic triolborates prepared by Yamamoto and Miyaura et al., and borate complexes of 1,3,5-cyclohexanetriol were good reactants in Suzuki–Miyaura cross-coupling reactions, the fact that a complex between *scyllo*-inositol and aryl boronic acid poorly reacted with aryl bromides under the same conditions gave an intriguing result and suggested that *scyllo*-inositol was an efficient protecting group for organoboronic acids under Suzuki–Miyaura coupling reaction conditions.

The preparation of SABC was so concise that each compound was merely mixed in hot water. In a typical procedure, a solution of an equimolar ratio of aryl boronic acid and hydroxide and 0.6 molar equivalents of *scyllo*-inositol in water was stirred at reflux for 1 h[7] (Table 2). After cooling to room temperature, alcoholic solvents such as methanol or ethanol, in which *scyllo*-inositol was hardly soluble, were added to the solution, and insoluble material was removed by filtration. The filtrate was concentrated, and the

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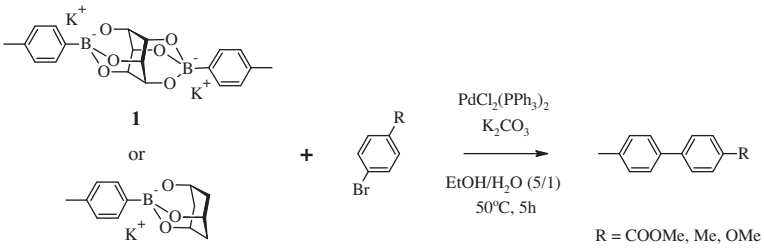
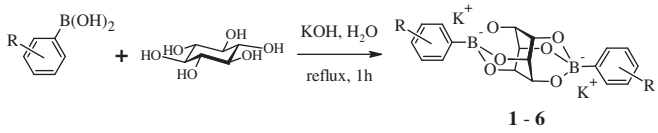
Table 1
Suzuki–Miyaura cross-coupling reaction with **1** or **1a**



Entry	Starting material	R	Yield[a] (%)
i	**1**	COOMe	13
ii	**1a**	COOMe	90
iii[b]	**1a**	COOMe	86
iv	**1**	Me	9
v[b]	**1a**	Me	81
vi	**1**	OMe	5[c]
vii[b]	**1a**	OMe	56
viii[b,d]	**1a**	OMe	79

[a] Isolated yield.
[b] Without base.
[c] Determined by crude ^{1}H NMR.
[d] $Pd(OAc)_2$ in DMF/H_2O at rt for 4 h.

Table 2
Preparation of SABC



Compound	R	Stable hydrate form	Yield[a] (%)
1	*p*-Me	$3H_2O$	84
2	H	$3H_2O$	82
3	*p*-Br	$4H_2O$	89
4	*m*-Br	$5H_2O$	87
5	*o*-Br	$4H_2O$	86
6	3,5-diBr	$3H_2O$	84

[a] Isolated yield.

residue was washed with toluene several times to yield SABCs in satisfactory purity.[8] Compounds obtained through this procedure were generally hydrates, and dehydration was accomplished by heating SABC powder in an oven at 105–150 °C for several hours.[9] The anhydrides were gradually hydrated in air. When anhydrous SABC was stored at humidity levels of 10–40%, stable tri- to penta-hydrates were formed. It should be noted that SABC decomposes readily under acidic conditions, in contrast to its remarkable stability toward air, water and heat. SABC gradually decomposed to *scyllo*-inositol and the corresponding aryl boronic acid in an aqueous solution at pH 4-5 and instantly decomposed at pH 2–3.

The characterization of compounds **1**–**6** was confirmed by NMR analyses and X-ray crystal analysis.[10] First, the proton signals of the inositol moieties appear in the range of δ 3.7–3.8 in the ^{1}H NMR spectra, notably shifted to the higher magnetic field region as compared to that of intact *scyllo*-inositol (δ 2.9). Next, the ^{11}B NMR signals of **1**–**6** in the range of δ 1.9–2.4 support the formation of tetrahedral borate species. Finally, a single crystal X-ray structural analysis of **3** crystallized from ethanol confirms the chemical structure of the inositol-induced aryltrialkoxyborate. In Figure 1, an ORTEP plot shows the half structure of **3** because of its symmetry and the packing model reveals the whole structure of the compound: two 4-bromophenylborates are bridged by a cyclohexane ring. The C–B bond length (1.62 Å) is similar to that (1.60 Å) of a cyclic triolborate, $(NBu_4)[C_6H_5B(OCH_2)_3CCH_2CH_3]\cdot H_2O$, by Yamamoto et al.[4d] Additionally, the X-ray analysis shows that one B-O bond length is shorter than the other two B–O bond lengths. This may be due to the interaction between the potassium cation and the oxygen atom in the borate.

As shown in Table 1, SABC (**1**) poorly reacted with aryl bromides under Suzuki–Miyaura coupling conditions in the presence of catalytic $PdCl_2(PPh_3)_2$.[11] Thus, *scyllo*-inositol acted as an effective protecting group for organoboronic acids. The protection of boron functional groups in aryl boronic acids under coupling reaction conditions is useful in some cases, but only a few groups have focused on this area of research. Suginome et al. revealed that aryl boronic acids protected by 1,8-diaminonaphthalene (DAN) were useful for the preparation of heteroarenes by iterative elongation methods.[12] Furthermore, anthranilamide was established as both a protecting group for boronic acids in Suzuki–Miyaura coupling reactions and a directing group for ruthenium-catalyzed C–H-silylation reactions by the same group.[13] Burke et al. reported that methyliminodiacetic acid (MIDA) and chiral pinene-derived iminodiacetic acid (PIDA) were versatile protecting groups for organoboronic acids and performed concise total syntheses of natural compounds and pharmaceutical agents.[14] Therefore, protected boronic acids are useful for the synthesis of conjugated aromatic compounds.

To study the reactivity of aryl boronic acids protected by *scyllo*-inositol under Suzuki–Miyaura coupling conditions, competitive reactions of SABC and free aryl boronic acids with aryl bromide were conducted (Table 3). In the presence of SABC (**1**) and free phenylboronic acid, the coupling reaction with 1-bromo-4-*tert*-butylbenzene catalyzed by $PdCl_2(PPh_3)_2$, $PdCl_2(allyl)_2$, $PdCl_2(dppf)\cdot CH_2Cl_2$, or $Pd(OAc)_2$ preferentially produced the biaryl derived from free phenylboronic acid and 1-bromo-4-*tert*-butylbenzene, whereas few coupling products obtained from SABC were observed[15] (entry i in Table 3. For results obtained with catalysts other than $PdCl_2(PPh_3)_2$, see the Supplementary data). Switching the combination of reactants to SABC composed of phenylboronic acid (**2**) and 4-methylphenylboronic acid afforded primarily 4-*tert*-butyl-4′-methylbiphenyl (entry ii). Few coupling products between SABC and aryl bromides were observed, suggesting that the

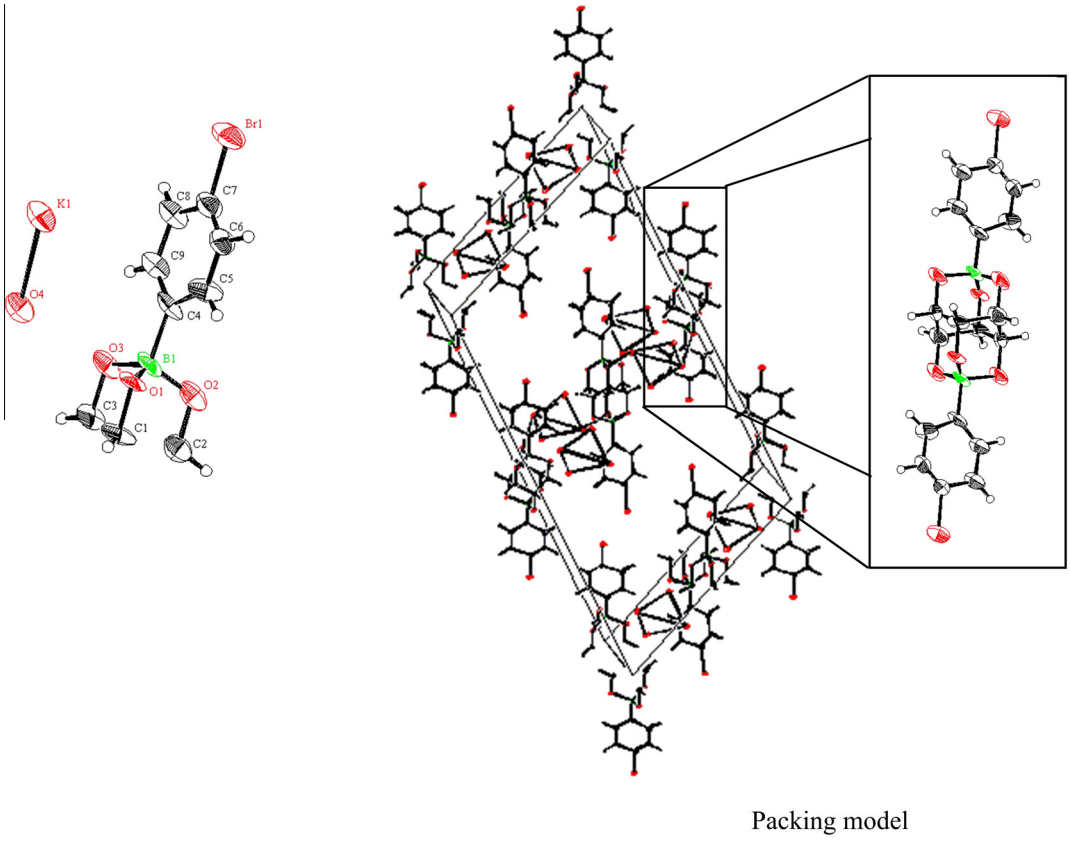
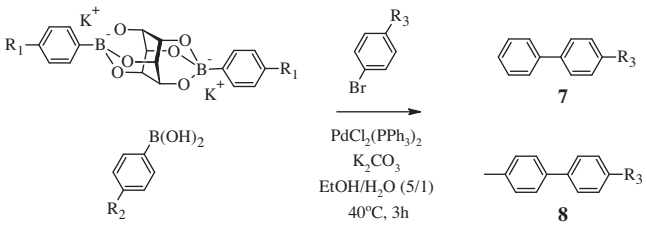


Figure 1. ORTEP and packing diagrams for **3**.

Table 3
Competitive reaction of SABC and aryl boronic acids



Entry		R_3 = *t*-Bu **7**:**8**[a]	R_3 = COOMe **7**:**8**[a]
i	R_1 = Me, R_2 = H	99.1:0.9	97.8:2.2
ii	R_1 = H, R_2 = Me	0.8:99.2	1.6:98.4

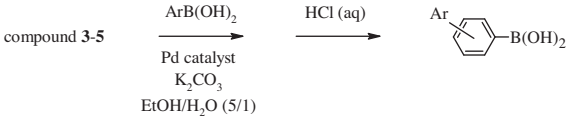
[a] The ratio was determined by HPLC analysis.

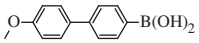
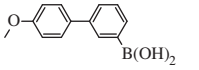
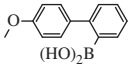
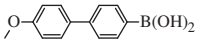
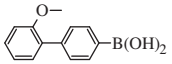
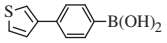
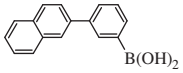
reaction between SABC and aryl bromides was slow compared to that of free boronic acids. Although the reaction between SABC **1** or **2** and methyl 4-bromobenzoate increased slightly, free boronic acids predominantly reacted with bromobenzoate in the same manner as that of 1-bromo-4-*tert*-butylbenzene. Hence, free aryl boronic acids preferentially reacted with aryl bromides in the presence of SABC.

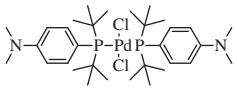
The protection of boronic acids worked well in an oligoarene synthesis conducted by Suginome et al. and a polyene synthesis performed by Burke et al., as mentioned above. These bi-functional compounds contained protected boronic acid moieties and reactive functional groups such as halides within the same molecule, which enabled efficient iterative coupling reactions. SABC containing halides were expected to show the same performance. Suzuki–Miyaura coupling reactions between free aryl boronic acids and SABCs containing aryl bromides were conducted (Table 4). The results showed that SABCs containing *para*- or *meta*-bromophenyl moieties (compound **3** or **4**, respectively) were effectively coupled with 4-methoxyphenylboronic acid in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$. Moreover, the deprotection of *scyllo*-inositol from the products by the addition of HCl to the solution gave the corresponding biaryl boronic acids in high yields[16] (entry i and ii in Table 4). The coupling reaction between a hindered *ortho*-bromophenyl containing SABC (**5**) and 4-methoxyphenylboronic acid did not proceed smoothly under the same conditions with $PdCl_2(PPh_3)_2$, and the biphenyl product was obtained in low yield (15% conversion yield). However, upon replacement of the catalyst with the more efficient $PdCl_2(Amphos)_2$[17], the conversion yield was improved to 70% as shown in entry iii. Although the yields were not as high as that observed in the HPLC analysis, the biaryl boronic acids could be isolated in moderate yield (entries iv–vii).[18] In detail, because the coupled borate intermediates between SABC and the aryl boronic acids were relatively soluble in water, the intermediate products were separated from other hydrophobic compounds and deprotection was performed by simple acidification of the aqueous solution, resulting in the precipitation of the desired conjugated aryl boronic acids. Compounds obtained through this procedure are expected to be useful for the synthesis of oligoarenes.

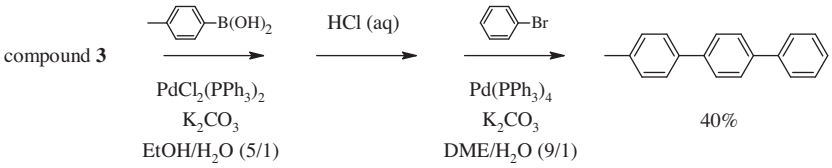
In addition, the cross-coupling reaction between compound **3** and 4-carbamoylphenylboronic acid, 4-dimethylaminophenylboronic acid, 4-formylphenylboronic acid, or 4-methoxycarbonylphenylboronic acid was conducted, but it was difficult to isolate the target boronic acids by silica-gel column chromatography. In each case

Table 4
Suzuki coupling of SABC with various aryl boronic acids



Entry	Starting material	$ArB(OH)_2$	Product	Yield (%)
i[a]	**3**	4-MeO-PhB(OH)$_2$		86[c]
ii[a]	**4**	4-MeO-PhB(OH)$_2$		78[c]
iii[b]	**5**	4-MeO-PhB(OH)$_2$		70[c]
iv[a]	**3**	4-MeO-PhB(OH)$_2$		49[d]
v[a]	**3**	2-MeO-PhB(OH)$_2$		49[d]
vi[b]	**3**	3-Thiophen-B(OH)$_2$		73[d]
vii[a]	**4**	2-Naph-B(OH)$_2$		63[d]

[a] Catalyzed by $PdCl_2(PPh_3)_2$.
[b] Catalyzed by $PdCl_2$(Amphos)$_2$. 
[c] Conversion yield determined by HPLC analysis.
[d] Isolated yield.



Scheme 1. Successive Suzuki–Miyaura coupling reactions with **3**.

the biaryl compound was extracted from acidic aqueous layer after the deprotection of *scyllo*-inositol (observed in the crude ^{1}H NMR spectrum) so that the cross-coupling reactions of **3** and the above aryl boronic acids were probably successful. The final isolation of the generated boronic acids was recognized as a potential difficulty in this method.

As an example of iterative cross-coupling reaction with SABC, 4-methyl-1,1′:4′,1″-terphenyl was synthesized from compound **3** (Scheme 1).[19] First, **3** was cross-coupled with 4-methylphenylboronic acid under Suzuki–Miyaura coupling reaction condition, and the *scyllo*-inostiol moiety was deprotected under acidic condition in the separation procedure. The organic extract layer was filtered through a short pad of silica-gel, and the evaporation residue of the filtrate was directly applied to the second coupling reaction with bromobenzene. After purification with silica-gel column chromatography, 4-methyl-1,1′:4′,1″-terphenyl was obtained in 40% from **3** after two cross-coupling reactions.

In summary, we demonstrated that *scyllo*-inositol and aryl boronic acids readily form unique air- and water-stable borate complexes with hydroxides in hot water. These novel complexes tolerated typical Suzuki–Miyaura cross-coupling reaction conditions catalyzed by palladium complexes with phosphine ligands. The competitive reaction of SABC and free aryl boronic acids with aryl bromides confirmed that *scyllo*-inositol could be used as a protecting group for boronic acids in Suzuki–Miyaura coupling reactions. In addition, Suzuki–Miyaura coupling reactions between brominated phenylboronic acids protected by *scyllo*-inositol and aryl boronic acids were successfully performed to afford several biaryl boronic acids. These results suggested, and in fact, SABC could be applied in successive cross-coupling reactions for the synthesis of π-conjugated molecule. Therefore, *scyllo*-inositol could be employed as a convenient and versatile protecting group for aryl boronic acids in Suzuki–Miyaura coupling reactions. Further applications of SABC will be presented in our future work.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.008.

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5. Weissbach, A. *J. Org. Chem.* **1958**, *23*, 329–330.
6. Compound **1** or **1a** was reacted with 1.8 equiv or 0.9 equiv, respectively, of aryl bromides in the presence of 2 equiv or 1 equiv, respectively, of K_2CO_3 and catalytic amounts of $PdCl_2(PPh_3)_2$ (0.1 equiv or 0.05 equiv, respectively) in EtOH/H_2O (5/1) at 50 °C for 5 h (the base was removed in entries iii, v, and vii). In entry viii, compound **1a** was reacted with 0.9 equiv of 1-bromo-4-methoxybenzene catalyzed by 0.05 equiv of $Pd(OAc)_2$ in DMF/H_2O (5/1) at rt for 4 h.
7. As an example, the synthesis of compound **1** is described: *scyllo*-inositol (728 mg, 4.04 mmol), potassium hydroxide (413 mg, 7.36 mmol) and 4-methylphenylboronic acid (1.00 g, 7.36 mmol) were suspended in 15 mL of hot water. The resulting suspension was stirred under reflux for 1 h. Subsequently, the solution became transparent and was cooled to room temperature. In total, 150 mL of ethanol was added, and the solution was vigorously stirred to precipitate the product. The precipitates were removed by filtration, and the filtrate was concentrated at reduced pressure. The residue was washed with toluene several times and was dried in vacuo. The resulting white powder was dried at 150 °C in an oven until a constant mass was achieved, yielding **1** (1.41 g, 84%) as an anhydrate. The weight of the anhydrate gradually increased over time in air and became constant, producing the trihydrate.
   *Characterization data for compound **1**:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18 (s, 6H, Me), 3.73 (s, 6H, CH), 6.78 (d, 4H, Ph, J = 7.3 Hz), 7.24 (d, 4H, Ph, J = 7.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.07, 70.64, 126.08, 131.52, 132.20 (C–B was not observed); ^{11}B NMR (128 MHz, DMSO-d_6): δ 2.03; HR-ESI-MS: 379.1538 ($C_{20}H_{21}O_6B_2^-$, [M−2K+H]$^-$; calcd 379.1530); elemental analysis: calcd (%) for $C_{20}H_{24}O_8B_2K_2$ (as dihydrate): C 48.80, H 4.91; found: C 49.73, H 4.82. *For compound **2**:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.77 (s, 6H, CH), 6.90 (tt, 2H, Ph, J = 1.9, 7.3 Hz), 6.95–6.99 (m, 4H), 7.36 (dd, 4H, Ph, J = 1.6, 8.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 70.61, 123.75, 125.37, 132.18 (C–B was not observed); ^{11}B NMR (128 MHz, DMSO-d_6): δ 2.42. *For compound **3**:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 6H, CH), 7.10–7.12 (m, 4H, Ph), 7.28–7.31 (m, 4H, Ph); ^{13}C NMR (100 MHz, DMSO-d_6): δ 70.57, 117.31, 128.02, 134.54 (C–B was not observed); ^{11}B NMR (128 MHz, DMSO-d_6): δ 2.19; HR-ESI-MS: 506.9439 ($C_{18}H_{15}O_6B_2Br_2^-$, [M−2K+H]$^-$; calcd 506.9427); elemental analysis: calcd (%) for $C_{18}H_{20}O_9B_2Br_2K_2$ (as trihydrate): C 33.78, H 3.15; found: C 33.64, H 2.96. *For compound **4**:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.75 (s, 6H, CH), 6.94 (t, 2H, Ph, J = 7.3 Hz), 7.05–7.08 (m, 2H), 7.31 (d, 2H, Ph, J = 7.3 Hz), 7.47 (d, 2H, Ph, J = 2.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 70.60, 120.50, 126.30, 127.83, 130.71, 134.92 (C–B was not observed); ^{11}B NMR (128 MHz, DMSO-d_6): δ 1.90. *For compound **5**:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80 (s, 6H, CH), 6.82 (td, 2H, Ph, J = 1.8, 7.4 Hz), 6.97 (td, 2H, Ph, J = 1.2, 7.2 Hz), 7.19 (dd, 2H, Ph, J = 0.9, 7.8 Hz), 7.47 (dd, 2H, Ph, J = 1.8, 7.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 70.65, 124.36, 126.05, 128.75, 131.22, 135.52 (C–B was not observed); ^{11}B NMR (128 MHz, DMSO-d_6): δ 1.98. *For compound **6**:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 6H, CH), 7.29 (t, 2H, Ph, J = 2.1 Hz), 7.42 (d, 4H, Ph, J = 1.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 70.56, 120.75, 128.20, 133.63 (C–B was not observed); ^{11}B NMR (128 MHz, DMSO-d_6): δ 1.88; HR-ESI-MS: 662.7645 ($C_{18}H_{13}O_6B_2Br_4^-$, [M−2K+H]$^-$; calcd 662.7637).
8. The concentration of the alcoholic solvent to a minimal volume and storage at room temperature also led to the precipitation of SABC.
9. Nearly all of the SABCs were stable after heating at 150 °C for several hours (5 h); however, the SABC composed of phenylboronic acid (compound **2**) degraded slightly to *scyllo*-inositol and phenylboronic acid after heating at 150 °C for 4–5 h. Drying at 105 °C for a couple of hours did not affect the complex.
10. CCDC 971419 contains the supplementary crystallographic data of **3**. This data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
11. The use of $Pd(OAc)_2$, a ligand-free palladium complex, slightly increased yields of the coupling reaction between compound **1** and aryl bromides similar to the trend between entry vii and viii in Table 1. This phenomenon is under investigation.
12. (a) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758–759; (b) Iwadate, N.; Suginome, M. *Org. Lett.* **2009**, *11*, 1899–1902; (c) Iwadate, N.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 2548–2549; (d) Iwadate, N.; Suginome, M. *Chem. Lett.* **2010**, *39*, 558–560.
13. Ihara, H.; Koyanagi, M.; Suginome, M. *Org. Lett.* **2011**, *13*, 2662–2665.
14. For recent examples of iterative cross-coupling reactions with MIDA boronate esters, see (a) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717; (b) Lee, S. J.; Anderson, T. M.; Burke, M. D. *Angew. Chem. Int. Ed.* **2010**, *49*, 8860–8863; (c) Fujii, S.; Chang, S. Y.; Burke, M. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 7862–7864; For PIDA boronates, see (d) Li, J.; Burke, M. D. *J. Am. Chem. Soc.* **2011**, *133*, 13774–13777.
15. To a suspension of 10 mg of 1-bromo-4-*tert*-butylbenzene (0.047 mmol), 8.6 mg of phenylboronic acid (0.070 mmol), 16 mg of **1** (0.035 mmol, anhydride), and 9.7 mg of K_2CO_3 (0.070 mmol) in 1 mL of EtOH/H_2O (4/1), 1.7 mg of $PdCl_2(PPh_3)_2$ (0.0024 mmol) in 0.2 mL of EtOH/H_2O (4/1) was added. After stirring at 50 °C for 3 h, 0.1 mL of the reaction suspension was centrifugally evaporated. In total, 0.1 mL of sat. $NaHCO_3$ aqueous solution and 0.3 mL of hexane/EtOAc (9/1) were added to the residue, and the mixture was shaken vigorously and centrifuged again. The organic supernatant (0.2 mL) was collected and centrifugally evaporated. The residue was dissolved in MeCN and was analyzed by HPLC.
16. *For entry i:* compound **3** (50 mg, 0.076 mmol, tetrahydrate), 4-methoxyphenylboronic acid (46 mg, 0.30 mmol), K_2CO_3 (42 mg, 0.30 mmol), and 6 mg of $PdCl_2(PPh_3)_2$ (0.009 mmol) were suspended in 2 mL of degassed EtOH/H_2O (5/1) under a N_2 atmosphere. After stirring at 50 °C for 4 h, 18 mL of EtOH was added, and 2 mL of the suspension was collected and quenched with 0.2 mL of 1 M HCl. The suspension was evaporated, and the residue was dissolved in 60% MeCN (aq), and was analyzed by HPLC with the previously prepared sample. *For entry iii:* to a suspension of 50 mg of **5** (0.076 mmol, tetrahydrate), 46 mg of 4-methoxyphenylboronic acid (0.30 mmol), and 42 mg of K_2CO_3 (0.30 mmol) in 6 mL of degassed EtOH/H_2O (5/1), 6.5 mg of $PdCl_2(Amphos)_2$ (0.0092 mmol) in 0.1 mL of the same solvent was added under a N_2 atmosphere. After stirring at 50 °C for 5 h, 14 mL of EtOH was added, and the suspension was worked up in the same manner as entry i and analyzed by HPLC.
17. (a) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787–1789; (b) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104–5112.
18. The procedure for entry v is shown as an example: compound **3** (150 mg, 0.228 mmol, tetrahydrate), 2-methoxyphenylboronic acid (139 mg, 0.912 mmol), K_2CO_3 (126 mg, 0.912 mmol), and $PdCl_2(PPh_3)_2$ (19 mg, 0.027 mmol) were placed in a flask under a N_2 atmosphere. Degassed EtOH/H_2O (5/1; 3 mL) was added, and the reaction mixture was stirred at 50 °C for 4 h. The solvent was removed under reduced pressure. Hexane/EtOAc (1/1) was added, and the residue was extracted with water. To the aqueous layer, 1 M HCl was added dropwise until the pH was approximately 2, and the resulting mixture was extracted twice with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1→1/1) to give 51 mg of the biaryl compound (49%). All of the products gave satisfactory ^{1}H and ^{13}C NMR data (see the Supplementary data).
19. The reaction mixture containing compound **3** (300 mg, 0.456 mmol, tetrahydrate), 4-methylphenylboronic acid (248 mg, 1.82 mmol), K_2CO_3 (251 mg, 1.82 mmol), and $PdCl_2(PPh_3)_2$ (38 mg, 0.055 mmol) in EtOH/H_2O (5/1; 6 mL) was stirred at 50 °C for 4 h under a N_2 atmosphere. After cooled to room temperature, the solution was diluted with 50 mL of EtOH and passed thorough celite and concentrated. Hexane/EtOAc (1/1) was added and extracted with water twice. To the aqueous layer, 1 M HCl was added dropwise until the pH was approximately 2, and the resulting suspension was extracted twice with EtOAc. The combined organic layer was dried with Na_2SO_4 and passed through a short pad of silica-gel and concentrated in vacuo. To a suspension of the residue, K_2CO_3 (251 mg, 1.82 mmol) and $Pd(PPh_3)_4$ (32 mg, 0.027 mmol) in degassed DME/H_2O (9/1; 6 mL) under a N_2 atmosphere, bromobenzene (0.142 mL, 1.37 mmol) was added. After stirring at reflux for 6 h, the reaction solution was cooled to room temperature, diluted with EtOAc, and passed through celite. The filtrate was washed with water and brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane→hexane/diethylether = 98/2) to give 88 mg of 4-methyl-1,1′:4′,1″-terphenyl (40% from **3** after 2 steps) as a white powder. Mp: 205–207 °C (lit.[20a] 206–208 °C). The ^{1}H and ^{13}C NMR spectra corresponded to literature data.[20b]
20. (a) Miguez, J. M. A.; Adrio, L. A.; Sousa-Pedrares, A.; Vila, J. M.; Hii, K. K. *J. Org. Chem.* **2007**, *72*, 7771–7774; (b) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 19505–19511.