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Site-Selective Suzuki–Miyaura Reaction of 6,8-Dibromoflavone

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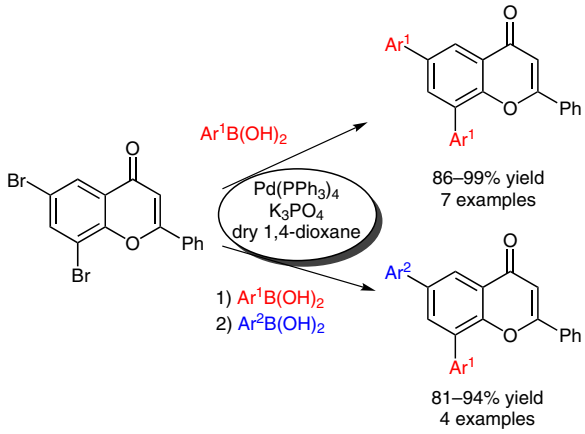

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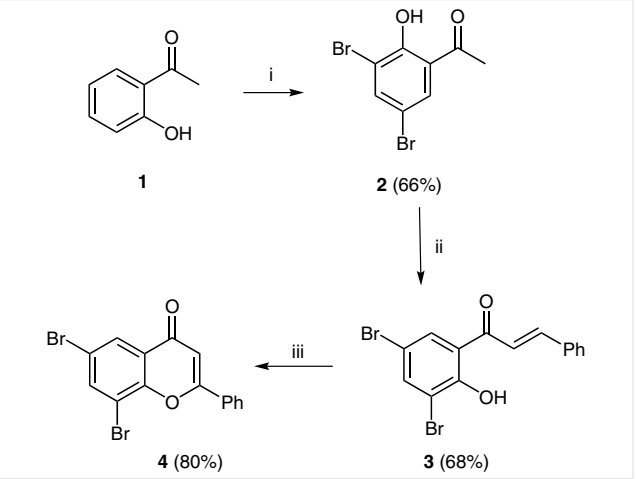
Abstract 8-Aryl- and 6,8-diarylflavones were prepared by Suzuki–Miyaura reactions of 6,8-dibromoflavone. In spite of the greater steric hindrance, the first attack proceeded with good site selectivity at position 8.

Key words palladium, catalysis, flavones, Suzuki–Miyaura reaction, regioselectivity

Flavones (2-aryl-4*H*-1-benzopyran-4-ones) are widespread in nature as plant metabolites.[1] Versatile biological activities of flavone derivatives were observed, for example, antioxidant, antimicrobial, antiproliferative, anti-inflammatory, and central nervous system protective properties.[1–4] Most syntheses of flavones are based on the corresponding chromone (4*H*-1-benzopyran-4-one) core structure by conventional methods.[2,3]Arylated flavone derivatives show different biological activities, for example, cytotoxic, antibacterial, antiviral, anti-inflammatory, enzyme inhibition, and even DNA repairing properties have been displayed.[5] The Suzuki–Miyaura reaction, a palladium-catalyzed C–C coupling of boronic acids with aryl halides, triflates, or tosylates, was first published in 1979.[6] The advantages of the Suzuki coupling include the commercial availability of arylboronic acids, the mild reaction conditions, as well as the high functional group tolerance.[7] Several ligands and catalysts have been reported.[8] Due to the difference between their reactivity, the chemoselectivity depends on the type of the leaving groups (ArI > ArBr > ArOTf > ArCl > ArOTs).[9] In the case of dihalogenated substrates containing only one type of leaving group, the regioselectivity is controlled by electronic and steric factors.[10] The regioselectivity of palladium(0)-catalyzed cross-coupling reactions of substances can be predicted with a simple guide suggested by Handy and Zhang based on ^{1}H NMR spectroscopic chemical shift values.[10c] The Suzuki–Miyaura coupling has been recently employed to modify the flavone core structure.[11] Herein, we wish to report what are, to the best of our knowledge, the first site-selective Suzuki–Miyaura reactions of 6,8-dibromoflavone. These reactions provide a convenient approach to a variety of novel arylated flavone derivatives.

Bromination of commercially available 2′-hydroxyacetophenone (**1**) gave 3′,5′-dibromo-2′-hydroxyacetophenone (**2**) in good yield.[12] Product **2** was converted into dibromochalcone **3** by Claisen–Schmidt condensation.[13] The ring-closure of **3**, carried out in the presence of a catalytic amount of iodine in hot dimethyl sulfoxide,[14] resulted in the corresponding dibromoflavone **4** (Scheme 1).



Scheme 1 Synthesis of **4**. *Reagents and conditions*: (i) **1** (1.0 equiv), Br_2 (2.2 equiv), $AlCl_3$ (1.5 equiv), DCE, 84 °C, 2 h; (ii) PhCHO (1.5 equiv), KOH (4.0 equiv), EtOH–H_2O, 20 °C, overnight; (iii) I_2 (cat.), DMSO, 180 °C, 15 min.

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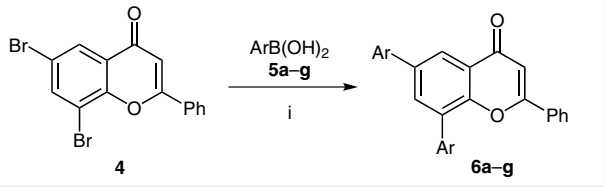
The Suzuki–Miyaura reaction of **4** with arylboronic acids **5a**–**g** (3.0 equiv) afforded 6,8-diarylflavones **6a**–**g** in very good yields (Scheme 2, Table 1).[15] Both electron-poor and electron-rich arylboronic acids were successfully employed. However, boronic acids with an electron-donating group reacted more rapidly; others with electron-withdrawing substituents needed more time and higher temperatures to achieve a full conversion. The reactions were carried out in abs.1,4-dioxane at 90–100 °C using $Pd(PPh_3)_4$ (6 mol%) as catalyst and K_3PO_4 (3.0 equiv) as base. Monitoring of the reaction by TLC revealed that the monoarylated product was initially formed. Before all the starting material **4** was consumed, the diarylated product started to be formed until full conversion of **4**.



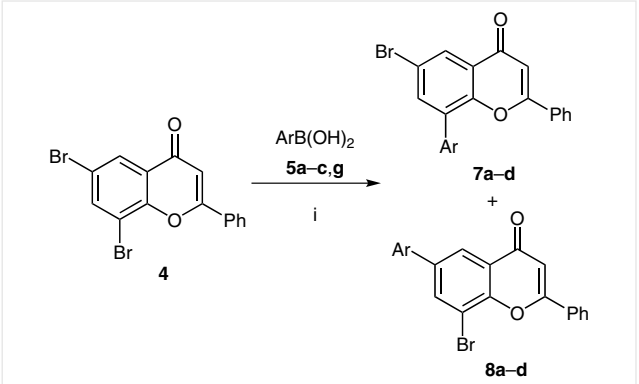
Scheme 2 Synthesis of **6a**–**g**. *Reagents and conditions*: (i) **4** (1.0 equiv), **5a**–**g** (3.0 equiv), $Pd(PPh_3)_4$ (6 mol%), K_3PO_4 (3.0 equiv), dry 1,4-dioxane, 90–100 °C.

Table 1 Synthesis of **6a**–**g**

Entry	5	6	Ar	Temp (°C)	Time (h)	Yields 6 (%)[a]
1	**5a**	**6a**	4-MeC_6H_4	90	2	93
2	**5b**	**6b**	4-$MeOC_6H_4$	90	5	86
3	**5c**	**6c**	3,4-$(MeO)_2C_6H_3$	100	15	99
4	**5d**	**6d**	Ph	100	15	96
5	**5d**	**6e**	4-ClC_6H_4	100	24	83
6	**5f**	**6f**	4-FC_6H_4	100	24	95
7	**5f**	**6g**	4-$F_3CC_6H_4$	100	24	94

[a] Yields refer to pure isolated products.

6,8-Dibromoflavone (**4**) was also successfully transformed into 6-bromo-8-arylflavones **7a**–**d** by a Suzuki–Miyaura reaction using arylboronic acids **5a**–**c**,**g**. The reactions were performed in moderate to good yields and with very good site selectivity (Scheme 3, Table 2).[16a] Both electron-poor and electron-rich arylboronic acids were successfully used. According to Handy and Zhang's method, which use the ^1H NMR chemical shifts of the nonhalogenated parent compounds in case of polyhalogenated heteroaromatics, the predicted regioselectivity of 6,8-dibromoflavone (**4**) is C8 > C6. In this case, the electronic difference is quite small as showed by a modest ($\Delta\delta$ = 0.15) chemical shift[16b] difference between C6 and C8, but still sufficient to direct the first coupling to the more electron-deficient C8 site. However, we observed that, besides the desired products **7a**–**d**, unreacted 6,8-dibromoflavone (**4**), the corresponding diarylated, and the isomeric monocoupled byproducts **8a**–**d** were also present in small amounts in the crude reaction mixture (vide infra). Products **7a**–**d** were isolated in pure form by chromatography. The best yields were obtained using only 1.2 equivalents boronic acid with $Pd(PPh_3)_4$ (6 mol%) in dry 1,4-dioxane at a temperature of 80 °C.



Scheme 3 Synthesis of **7a**–**d**. *Reagents and conditions*: (i) **4** (1.0 equiv), **5a**–**c**,**g** (1.2 equiv), $Pd(PPh_3)_4$ (6 mol%), K_3PO_4 (2.0 equiv), dry 1,4-dioxane, 80 °C, 48 h.

Table 2 Synthesis of **7a**–**d**

Entry	5	7	Ar	Yield of 7 and 8 (%)[a]
1	**5a**	**7a**	4-MeC_6H_4	47
2	**5b**	**7b**	4-$MeOC_6H_4$	59
3	**5c**	**7c**	3,4-$(MeO)_2C_6H_3$	57[b]
4	**5g**	**7d**	4-$F_3CC_6H_4$	57

[a] Yields refer to pure isolated products.
[b] Product **8c** was isolated in pure form (12% yield).

All products were characterized by spectroscopic methods (NMR, IR, MS, HRMS). The structural characterization of products **7a**–**d** was supported by 2D NMR experiments (HMBC, NOESY). In the case of **7c**, besides the pure isolated product **7c**, a fraction containing a 4.7:1 mixture of **7c** along with its isomeric byproduct **8c** was isolated. This allowed the unequivocal identification of **8c** by NOESY measurements (Figure 1). The structure of **7c** was independently confirmed by X-ray crystal-structure analysis (Figure 2).[17]

The Suzuki–Miyaura reaction of monoarylated derivatives **7c** and **7d** with arylboronic acids **5a** and **5e** (2.0 equiv) provided 6,8-diarylflavones **9a**–**d** (Scheme 4, Table 3).[18,19] The reactions were carried out at 100 °C and resulted in high yields. No marked electronic effects of the substituents on the yield were observed.

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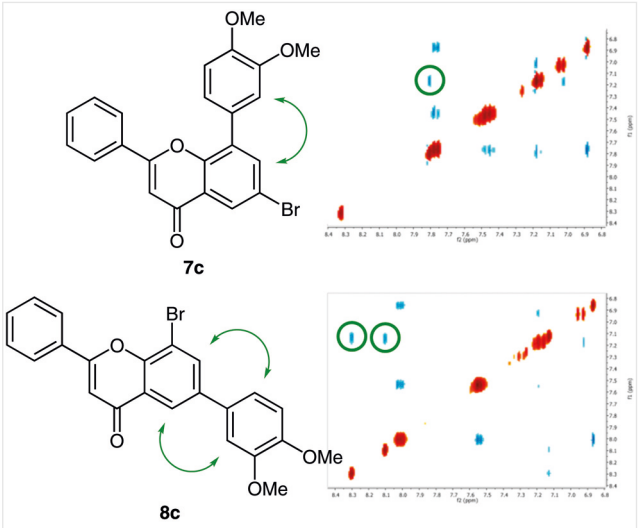


Figure 1 NOESY measurements of **7c** and **8c**

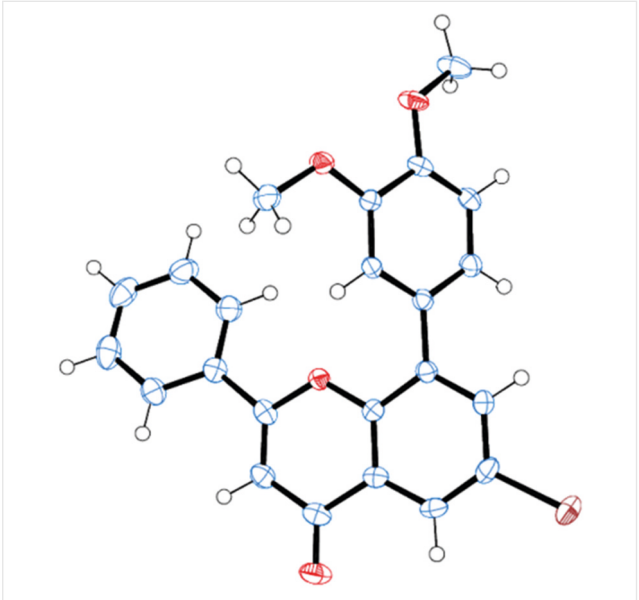
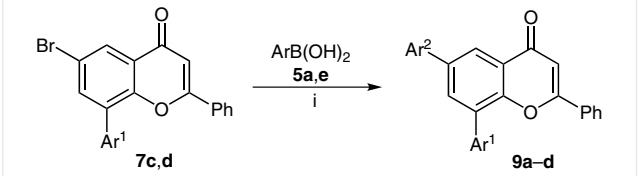


Figure 2 Crystal structure of **7c**[17]



Scheme 4 Synthesis of **9a–d**. *Reagents and conditions*: (i) **7c**,**d** (1.0 equiv), **5a**,**e** (2.0 equiv), $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (2.5 equiv), dry 1,4-dioxane, 100 °C, 2 h.

Table 3 Synthesis of **9a–d**

Entry	7	5	9	R^1	R^2	Yields of **9** (%)[a]
1	**7c**	**5a**	**9a**	3,4-$(MeO)_2C_6H_3$	4-MeC_6H_4	93
2	**7c**	**5e**	**9b**	3,4-$(MeO)_2C_6H_3$	4-ClC_6H_4	81
3	**7d**	**5a**	**9c**	4-$F_3CC_6H_4$	4-MeC_6H_4	89
4	**7d**	**5e**	**9d**	4-$F_3CC_6H_4$	4-ClC_6H_4	94

[a] Yields refer to pure isolated products

In conclusion, we have reported the synthesis of a variety of arylated flavones by site-selective Suzuki–Miyaura reactions of 6,8-dibromoflavone. Various boronic acids were reacted smoothly under mild conditions, providing different mono-/bis-/diarylated derivatives of flavone in good to excellent yields. The regioselectivity of 6,8-dibromoflavone was predicted by Handy and Zhang's method, however, the method was developed based on the reactions of polyhalogenated heteroaromatics and ^{1}H NMR chemical shifts of their the nonhalogenated parent compounds. The first attack occurred at the more electron-deficient center C8, providing 8-monoarylflavones in good yields. The second bromide (C6) also could take part in the coupling reaction, although it requires more vigorous conditions as our experiments showed. In case of the synthesis of symmetrically arylated compounds the cross-coupling took place for longer time using electron-poor boronic acids. However, the reaction of 8-monoarylflavones with different boronic acids did not show electronic effects of the substituents of the boronic acid.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560633.

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(15) **Procedure for Synthesising 6,8-Diarylflavone Derivatives 6a–g**
To a mixture of 6,8-dibromoflavone (**4**, 95 mg, 0.25 mmol), K_3PO_4 (160 mg, 0.75 mmol), and boronic acid **5** (0.75 mmol) in dry dioxane (4 mL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) was added in a dried pressure tube under argon. The reaction mixture was stirred and heated in an aluminum heating block till full conversion. The solvent was removed under reduced pressure, and the solid mixture was dissolved in CH_2Cl_2. The solution was submitted to adsorptive filtration on silica gel using CH_2Cl_2 as eluent to remove the inorganic compounds. The CH_2Cl_2 was evaporated; the residue was washed two times with acetone then filtered to give the pure cross-coupled product **6**.

(16) (a) **Procedure for Synthesising 8-Aryl-6-bromoflavone Derivatives 7a–d**
To a mixture of 6,8-dibromoflavone (**4**, 95 mg, 0.25 mmol), K_3PO_4 (106 mg, 0.5 mmol), and boronic acid **5** (0.30 mmol) in dry dioxane (4 mL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) was added

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in a dried pressure tube under argon. The reaction mixture was stirred and heated at 80 °C for 48 h in an aluminum heating block. The solvent was removed in vacuum, and the solid mixture was dissolved in CH_2Cl_2. The solution was submitted to adsorptive filtration on silica gel using CH_2Cl_2 as eluent to remove the inorganic compounds. The eluted solution was concentrated then the mixture was purified by column chromatography (eluent: heptane–EtOAc mixture; the ratio is given at the compound) to give the monosubstituted product.

(b) **^{1}H NMR Spectroscopic Data of Flavone**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.9 Hz, 1 H, 5-H), 7.97–7.89 (m, 2 H, 2′,6′-H), 7.70 (t, *J* = 8.4 Hz, 1 H, 7-H), 7.58 (d, *J* = 8.3 Hz, 1 H, 8-H), 7.56–7.50 (m, 3 H, 3′,4′, 5′-H), 7.43 (t, *J* = 7.5 Hz, 1 H, 6-H), 6.83 (s, 1 H, 3-H).

(17) CCDC-1052200 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

(18) **Procedure for Synthesizing Differently Substituted 6,8-Diarylflavone Derivatives 9a–d**

To a mixture of 8-aryl-6-bromoflavones **7c**,**d** (0.10 mmol), K_3PO_4 (54 mg, 0.25 mmol), and boronic acid **5a**,**e** (0.20 mmol) in dry dioxane (4 mL), $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol) was added in a dried pressure tube under argon. The reaction mixture was stirred and heated at 100 °C for 2 h in an aluminum heating block. The solvent from the crude reaction mixture was removed in vacuum, and the solid residue was dissolved in CH_2Cl_2. The solution was submitted to adsorptive filtration on silica gel using CH_2Cl_2 as eluent to remove the inorganic compounds. The eluted solution was concentrated, then the mixture was purified by column chromatography (eluent: heptane–EtOAc mixture; the ratio is given at the compound) to give the nonsymmetric diarylated product.

(19) **6,8-Bis(4-methylphenyl)flavone (6a)**

Starting with **4** (95 mg, 0.25 mmol), K_3PO_4 (160 mg, 0.75 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol, 6 mol%), (4-methylphenyl)boronic acid (**5a**, 102 mg, 0.75 mmol), and 1,4-dioxane (4 mL), **6a** was isolated as a light yellow solid (94 mg 93%), mp 247.0–248.5 °C. ^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ = 8.44 (d, *J* = 2.7 Hz, 1 H, 5-H), 7.96 (d, *J* = 2.4 Hz, 1 H, 7-H), 7.82–7.79 (m, 2 H, 2′,6′-H), 7.64–7.59 (m, 4 H, 2″,6″-H, 2‴,6‴-H), 7.49.7.46 (m, 3 H, 3′,5′-H, 4′-H), 7.37 (d, *J* = 9.6 Hz, 2 H, 3‴,5‴-H), 7.27 (d, *J* = 9.6 Hz, 2 H, 3″,5″-H), 6.96 (s, 1 H, 3-H), 2.50 (s, 3 H, 4‴-CH_3), 2.42 (s, 3 H, 4″-CH_3). ^{13}C NMR (75 MHz, 298 K, $CDCl_3$): δ = 178.7 (C-4), 163.2 (C-2), 152.4 (C-8a), 138.1 (C-4″,4‴), 137.8 (C-6), 136.4 (C-8), 133.4 (C-7), 133.2 (C-1″), 132.3 (C-1‴), 131.6 (C-1′), 131.5 (C-4′), 129.7 (C-3″,5″), 129.5 (C-3‴,5‴), 129.1 (C-2‴,6‴), 129.0 (C-3′,5′), 127.0 (C-2″,6″), 126.3 (C-2′,6′), 124.5 (C-4a), 122.1 (C-5), 126.9 (C-3), 21.3 (4‴-CH_3), 21.1 (4″-CH_3). IR (ATR): ν = 1636, 1597, 1459, 1447, 1363, 1173, 812, 775, 687, 633, 502 cm^{-1}. GC-MS (EI, 70eV): *m/z* (%) = 402 (100) [M$^{+\bullet}$], 300, 229, 102. HRMS: *m/z* calcd for $C_{29}H_{22}O_2$: 402.16143; found: 402.16156.

6-Bromo-8-(3,4-dimethoxyphenyl)flavone (7c)

Starting with **4** (95 mg, 0.25 mmol), K_3PO_4 (106 mg, 0.5 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol, 6 mol%), (3,4-dimethylphenyl)boronic acid (**5c**, 55 mg, 0.30 mmol), and 1,4-dioxane (4 mL), **7c** was isolated as a white solid (62 mg 57%), mp 186.5–188 °C (eluent: heptane–EtOAc, 2:1). ^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ = 8.31 (d, 1 H, *J* = 2.4 Hz, 5-H), 7.80 (d, 1 H, *J* = 2.4 Hz, 7-H), 7.77–7.75 (m, 2 H, 2′,6′-H), 7.51–7.45 (m, 3 H, 3′,5′-H, 4′-H), 7.18–7.15 (m, 2 H, 2″,6″-H), 7.04 (d, *J* = 8.1 Hz, 1 H, 5″-H), 6.88 (s, 1 H, 3-H), 3.99 (s, 3 H, 4″-OCH_3), 3.88 (s, 3 H, 3″-OCH_3). ^{13}C NMR (75 MHz, 298 K, $CDCl_3$): δ = 177.1 (C-4), 163.3 (C-2), 151.9 (C-8a), 149.4 (C-3″), 148.7 (C-4″), 137.0 (C-7), 133.8 (C-1″), 131.8 (C-4′), 131.2 (C-1′), 129.0 (C-3′,5′), 127.3 (C-8), 126.9 (C-5), 126.2 (C-2′,6′), 125.6 (C-4a), 122.2 (C-6″), 118.6 (C-6), 112.6 (C-2″), 111.1 (C-5″), 106.9 (C-3), 55.9 (3″-OCH_3, 4″-OCH_3). IR: (ATR): ν = 3061, 2999, 2933, 2838, 1637, 1567, 1512, 1452, 1358, 1251, 1224, 1137, 1022, 882, 780, 694, 670, 637, 589 cm^{-1}. GC-MS (EI, 70eV): *m/z* (%) = 436 [M$^{+\bullet}$], 438 [M$^{+\bullet}$ + 2], 293, 291, 184, 102. HRMS: *m/z* calcd for $C_{23}H_{17}O_4{}^{79}Br$: 436.03047; found: 436.03046; *m/z* calcd for $C_{23}H_{17}O_4{}^{81}Br$: 438.02843; found: 438.02866.

6-(4-Chlorophenyl)-8-(3,4-dimethoxyphenyl)flavone (9b)

Starting with **7c** (44 mg, 0.10 mmol), K_3PO_4 (42 mg, 0.2 mmol), $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol, 5 mol%), (4-chlorophenyl)boronic acid (**5e**, 31 mg, 0.20 mmol), and 1,4-dioxane (4 mL), **9b** was isolated as a light yellow solid (38 mg, 81%), mp 228–229 °C (eluent: heptane–EtOAc, 2:1). ^{1}H NMR (300 MHz, 298 K, $CDCl_3$): δ = 8.40 (d, *J* = 3.0 Hz, 1 H, 5-H), 7.90 (d, *J* = 3.0 Hz, 1 H, 7-H) 7.82–7.90 (m, 2 H, 2′,6′-H), 7.64 (d, *J* = 8.1 Hz, 2 H, 2″,6″-H,) 7.52–7.43 (m, 5 H, 3′,5′-H, 4′-H, 3‴,5‴-H), 7.25–7.21 (m, 2 H, 2‴,6‴-H), 7.07 (d, *J* = 8.1 Hz, 1 H, 5‴-H), 6.93 (s, 1 H, 3-H), 4.00 (s, 3 H, 4‴-OCH_3), 3.90 (s, 3 H, 3″-OCH_3). ^{13}C NMR (75 MHz, 298 K, $CDCl_3$): δ = 178.4 (C-4), 163.2 (C-2), 152.6 (C-8a), 149.3 (C-3‴), 148.8 (C-4‴), 137.7 (C-1″), 136.9 (C-6), 134.1 (C-4″), 133.1 (C-7), 132.4 (C-1‴), 131.8 (C-4′), 131.5 (C-1′), 129.2 (C-3′,5′), 129.1 (C-3″,5″), 128.6 (C-8), 128.4 (C-2″,6″), 126.3 (C-2′,6′), 124.7 (C-4a), 122.3 (C-5), 122.2 (C-6‴), 112.9 (C-2‴), 111.2 (C.5‴), 106.9 (C-3), 56.0 (3‴-OCH_3, 4‴-OCH_3). IR (ATR): ν = 2957, 2834, 1640, 1514, 1461, 1243, 1225, 1141, 1029, 821, 688 cm^{-1}. GC-MS (EI, 70eV): *m/z* (%) = 468 [M$^{+\bullet}$], 470 [M$^{+\bullet}$ + 2], 425, 323, 189, 102. HRMS: *m/z* calcd for $C_{29}H_{21}O_4{}^{35}Cl$: 468.11229; found: 468.11195.

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