Synthesis S. Jordán et al. Paper

Synthesis of 6,7-Dibromoflavone and Its Regioselective Diversification via Suzuki–Miyaura Reactions

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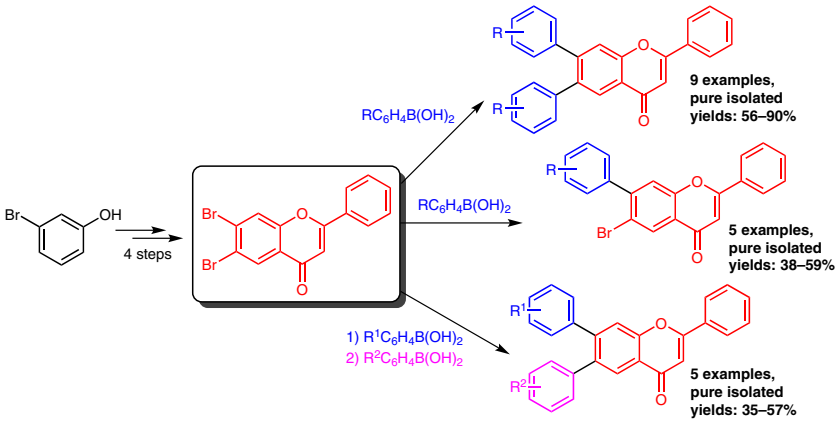
Dedicated to the memory of Prof. Tamás Patonay



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Abstract The first synthesis pathway to 6,7-dibromoflavone and its transformations to 7-aryl-6-bromo- and 6,7-diarylflavones by Suzuki–Miyaura reactions are presented. Due to the different electronic effects of bromo substituents, the first attack proceeded with good site selectivity at position 7.

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

Flavones (2-aryl-4*H*-1-benzopyran-4-ones) are common molecules in nature mostly as plant metabolites.[1] Flavone derivatives show versatile biological activities, e.g. antioxidant, antimicrobial, antiproliferative, and anti-inflammatory properties, and central nervous system protective effects were also detected.[1–4] The syntheses of flavones are mostly based on the corresponding chromone (4*H*-1-benzopyran-4-one) core structure by conventional methods.[2,3]

Different biological activities were observed in the case of arylated flavone derivatives, e.g. antiviral, antibacterial, anti-inflammatory, enzyme inhibition, cytotoxic and even DNA repairing properties have been reported.[5] The Suzuki–Miyaura reaction[6] is a palladium-catalyzed C–C coupling reaction using boronic acids and an aryl halide, triflate, or tosylate substrate that may be a suitable method for synthesizing arylated flavones.

Besides the commercial availability of common boronic acids, the advantages of the Suzuki–Miyaura reaction over other palladium-catalyzed reactions are high functional group tolerance and mild reaction conditions.[7] The chemoselectivity of the reaction depends on the type of the leaving groups, following the order of reactivity: Ar–I > Ar–Br > Ar–OTf > Ar–Cl > Ar–OTs.[8] A successful coupling reaction can be carried out with several type of catalysts and ligands.[9]

In the Suzuki–Miyaura reaction of dihalogenated materials, containing only one type of leaving group, the regioselectivity is controlled by steric and electronic factors.[10] Handy and Zhang suggested a simple guide, based on ^{1}H NMR spectroscopic chemical shift values, suitable to predict the regioselectivity of palladium(0)-catalyzed cross-coupling reactions.[10d] In the last few years, regioselective Suzuki–Miyaura coupling has become a useful approach to increase the diversity of arylated flavone derivatives providing new differently substituted flavones.[11]

In Nature many plants are known that show different biological effects and a number contain 6,7-disubstituted flavonoid compounds (Figure 1). For example, gan cao,[12] also known as licorice, includes roots and or rhizomes of *Glycyrrhiza inflata* Batal, *G. uralensis* Fisch, and *G. glabra* L. is recorded in Chinese Pharmacopoeia. NQO1 and tumor angiogenesis assay suggested three effective flavonoids, one of them is licoflavone B, as being responsible for the chemopreventive effect. Its chemical and biological results indicated that flavonoids from the residue of gan cao are promising natural cancer chemopreventive agents with low toxicity. Another example is *G. sagittatum*[13] the roots of which have been traditionally used in the Peruvian Amazon as an anti-inflammatory, analgesic, and diuretic remedy, whereas the infusion from the leaves is used to treat asthma and anemia. Nowadays *G. sagittatum* is used as a component of a herbal medicine for the treatment of female infertility. From methanol and ethyl acetate extracts of this plant, 6-hydroxy-7,4′-dimethoxyflavone and 6,7,4′-tri-

methoxyflavone were isolated among other flavonoids. Moreover, one of the constituents of *M. erythrocalyx* Gagnep,[14] a plant growing in the central part of Thailand, is millettocalyxin B; and the bark of this plant has been used by the local people to treat stomach pain.

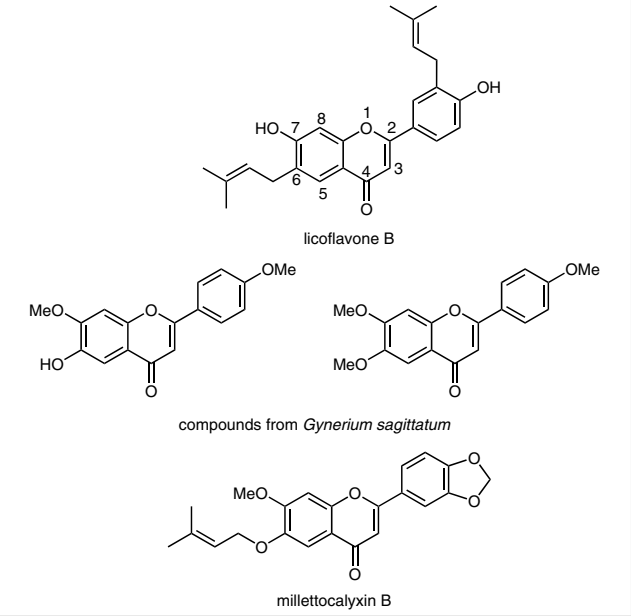
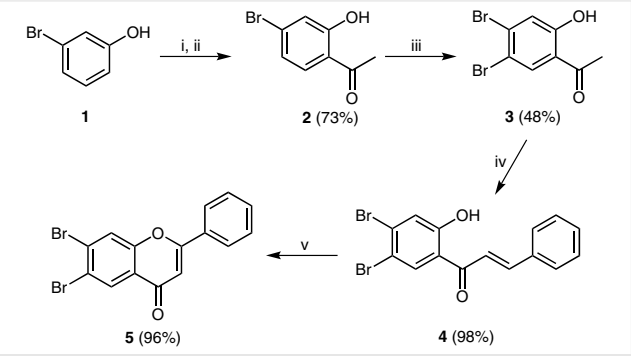


Figure 1 6,7-Disubstituted flavonoids from natural sources

In order to increase the members of this family, we planned to synthesize 6,7-dibromoflavone as a new substrate since its detailed procedure is not known in the literature according to our current knowledge. In this manner the synthesis and the transformation of 6,7-dibromoflavone can open a new gate to the synthesis of analogues of other 6,7-disubstituted flavone compounds for further biological assays.



Scheme 1 Synthesis of **5**. *Reagents and conditions*: (i) **1**, Ac_2O (6.88 equiv), anhyd NaOAc (2.11 equiv), reflux, 2.5 h; (ii) $AlCl_3$, 170 °C, 3 h; (iii) **2**, Br_2 (1.06 equiv), anhyd $ZnCl_2$ (2.20 equiv), CS_2, 0 °C–r.t., 24 h; (iv) **3**, PhCHO (1.1 equiv), 50% aq NaOH (4.0 equiv), EtOH, r.t., 24 h; (v) **4**, I_2 (0.06 equiv), DMSO, 180 °C, 15 min.

Herewith, we report the first synthesis of 6,7-dibromoflavone and its regioselective Suzuki–Miyaura reactions resulting in 6,7-diarylflavone derivatives. The acylation and Fries rearrangement of the commercially available 3-bromophenol (**1**) resulted in 4′-bromo-2′-hydroxyacetophenone (**2**). Its further bromination led to 4′,5′,-dibromo-2′-hydroxyacetophenone (**3**) in moderate yield, and this compound was transformed into dibromochalcone **4** by Claisen–Schmidt condensation.[15] Using a catalytic amount of iodine in hot dimethyl sulfoxide[16] the ring closure of **4** provided the corresponding dibromoflavone **5** in excellent yield (Scheme 1).

For the preparation of 4′,5′-dibromo-2′-hydroxyacetophenone (**3**) the key step is the bromination of acetophenone **2**. The optimization of this step was carried out by varying the solvent, the Lewis acid catalyst, and the amount of bromine (Table 1).

Table 1 Optimization of the Synthesis of **3**

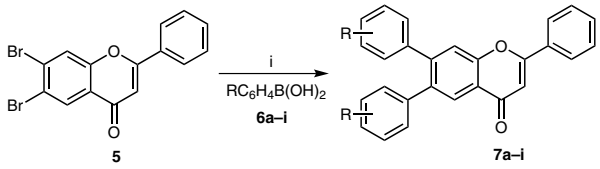
Br_2 (equiv)	Solvent	Lewis acid (equiv)	Yield[a] (%) of **3**
1.10	CS_2	$BF_3{\cdot}Et_2O$ (1.1)	3
1.10	benzene	$BF_3{\cdot}Et_2O$ (1.1)	18
1.10	benzene	$ZnCl_2$ (1.1)	12
1.10	CS_2	$ZnCl_2$ (1.1)	32
1.29	CS_2	$ZnCl_2$ (1.1)	24
1.10	CS_2	$ZnCl_2$ (2.2)	48

[a] Yields refer to pure isolated products.

Through these experiments, our aim was to find conditions under which the formation of the byproduct 3′,4′,5′-tribromo-2′-hydroxyacetophenone does not take place. This is essential because the separation of the byproduct is particularly difficult due to its low solubility in any kind of solvent. During our optimization efforts more solvents were examined and, as the results showed, the use of benzene gave full conversion of **2**, but the product was mainly 3′,4′,5′-tribromo-2′-hydroxyacetophenone. Therefore carbon disulfide was utilized and the amount of byproduct was decreased in all cases. The use of soft Lewis acids, such as boron trifluoride and zinc chloride, was examined and the yield of **3** significantly increased in the presence of zinc chloride in carbon disulfide. Increasing the equivalents of bromine up to 1.29 caused the formation of a larger amount of 3′,4′,5′-tribromo-2′-hydroxyacetophenone. Thus, acetophenone **3** was isolated in the highest yield when the amount of zinc chloride was raised to 2.2 equivalents and the bromine was added in 1.10 equivalents in carbon disulfide.

The Suzuki–Miyaura reaction of **5** with arylboronic acids **6a–i** (2.3 equiv) afforded 6,7-diarylflavones **7a–i** in moderate to good yields (Table 2).

Table 2 Synthesis of **7a–i**[a]



5 **7a–i**

6	7	R	Time (h)	Yield[b] (%) of 7
6a	**7a**	H	6	67
6b	**7b**	3-OMe	2.5	75
6c	**7c**	4-OMe	4	70
6d	**7d**	3-F	2.5	56
6e	**7e**	4-F	3.5	59
6f	**7f**	3-Cl	2.5	66
6g	**7g**	4-Cl	2.5	90
6h	**7h**	3-CF_3	5.5	72
6i	**7i**	4-CF_3	2	76

[a] Reaction conditions: (i) **5**, **6a–i** (2.3 equiv), $Pd(PPh_3)_4$ (10 mol%), 2 M aq Cs_2CO_3 solution (3.0 equiv), 1,4-dioxane/MeOH (5:1), argon atmosphere, 100 °C, 2–6 h.
[b] Yields refer to pure isolated products.

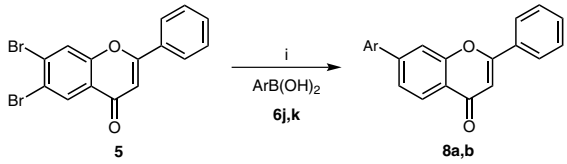
Both electron-rich and electron-poor arylboronic acids were successfully used. The electronic and steric effects of the boronic acid influenced the rate of the reaction. In every case the reaction was monitored until full conversion. First, the monocoupled molecule appeared, and then the diarylated **7a–i** product began to form before the substrate **5** completely disappeared. The reactions were carried out using $Pd(PPh_3)_4$ (10 mol%) as catalyst and Cs_2CO_3 (3.0 equiv) in aqueous solution as base in 1,4-dioxane/methanol mixture at 100 °C in a pressure tube.

Using boronic acids **6j**,**k** the corresponding monocoupled product formed, but instead of undergoing the second coupling, dehalogenation occurred which resulted in byproducts **8a**,**b** (Table 3). This result is explained by the considerable steric hindrance of the *ortho*-substituted arylboronic acids.

In order to check the role of the water and methanol in the dehalogenation process, the experiments with 2,6-dimethylphenylboronic acid were repeated. Performing the reaction in aqueous solution of 1,4-dioxane gave no reaction. However, if the reaction was repeated in methanolic solution of 1,4-dioxane without water the dehalogenated compound **8a** was isolated in 70% yield. Since, we were interested in the dehalogenation, we have checked the literature and found that the used of an alcohol (in our case MeOH) was the reason for the dehalogenation.[18]

6,7-Dibromoflavone (**5**) was also transformed into 7-aryl-6-bromoflavones **9a–e** in a Suzuki–Miyaura reaction using arylboronic acids **6e**,**i**,**l–n** (1.0 equiv). The reactions provided the corresponding products **9a–e** in moderate to

Table 3 Formation of **8a**,**b**[a]



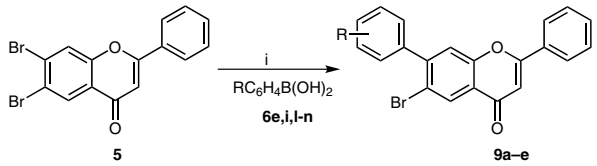
5 **8a,b**

6	8	Ar	Yield[b] (%) of 8
6j	**8a**	2,4-$Me_2C_6H_3$	39[c]
6k	**8b**	2,4,6-$Me_3C_6H_2$	43

[a] Formation of **8a**,**b** byproducts. Reaction conditions: (i) **5** (1.0 equiv), **6j**,**k** (2.3 equiv), $Pd(PPh_3)_4$ (10 mol%), 2 M aq Cs_2CO_3 solution (3.0 equiv), 1,4-dioxane/MeOH (5:1), argon atmosphere, 100 °C, 16 h.
[b] Yields refer to pure isolated products.
[c] Solvent: 1,4-dioxane/H_2O (5:1): no reaction; solvent: 1,4-dioxane/MeOH (5:1): 70% **8a**.

good yields and with very good site selectivity (Table 4). Both electron-poor and electron-rich arylboronic acids were successfully employed. The first coupling occurred in position 7 with very good site selectivity; the isomer byproduct was not isolated. The conversion was high, but after the purification only moderate yields were achieved due to the poor solubility of the products **9a–e**. The best yields were achieved using only 1.0 equiv boronic acid with $Pd(PPh_3)_4$ (4 mol%) in 1,4-dioxane/methanol mixture at 70 °C.

Table 4 Synthesis of **9a–e**[a]



5 **9a–e**

6	9	R	Time (h)	Yield[b] (%) of 9
6e	**9a**	4-F	4	53
6i	**9b**	4-CF_3	9	38
6l	**9c**	4-Me	4.5	57
6m	**9d**	4-*t*-Bu	6	49
6n	**9e**	4-Ph	4.5	59

[a] Reaction conditions: (i) **5**, **6e**,**i**,**l–n** (1.0 equiv), $Pd(PPh_3)_4$ (4 mol%), 2 M aq Cs_2CO_3 solution (3.0 equiv), 1,4-dioxane/MeOH (5:1), 70 °C, argon atmosphere, 4–9 h.
[b] Yields refer to pure isolated products.

According to Handy and Zhang's method, which uses the ^1H NMR chemical shifts of the non-halogenated parent compounds in the case of polyhalogenated heteroaromatics, the predicted regioselectivity of 6,7-dibromoflavone (**5**) is C-7 > C-6 ($\Delta\delta \cong 0.40$). In this case, the manifested electronic difference through the chemical shift differences between C-6 and C-7 is sufficient to direct the first coupling

to the more electron-deficient C-7 site. The first attack occurred at the more electron deficient center C-7, providing 7-monoaryl-6-bromoflavones in good yields. The second bromide (C-6) also could take part in the coupling reaction, although it requires more vigorous conditions as our experiments showed.

All products were characterized by spectroscopic methods. The structural characterization of products **9a–e** was supported by 2D NMR experiments (HMBC, NOESY) as well. Figure 2 shows the structure and the NOESY spectra of the product **9b**, which clearly proves the order of the coupling by the NOE effect of H-8 and H-2″.

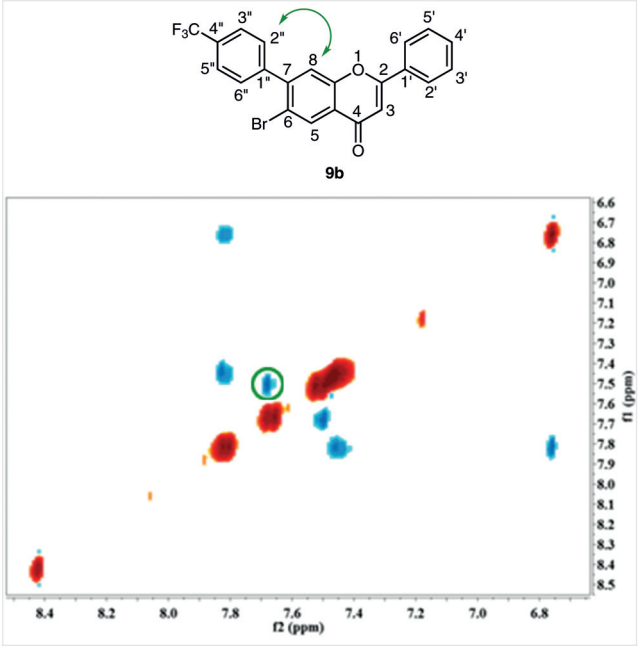
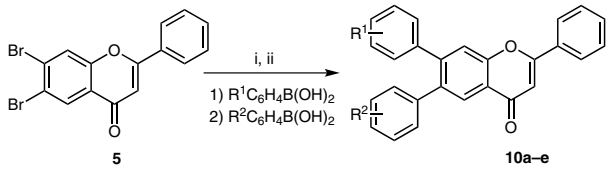


Figure 2 NOESY spectrum of **9b**

The Suzuki–Miyaura reaction of 6,7-dibromoflavone (**5**) was also studied as a one-pot reaction. In the first step, after the full conversion of substrate **5** with $Ar^1B(OH)_2$, the second type of boronic acid $Ar^2B(OH)_2$ was added along with extra 6 mol% catalyst. This method operated with very good regioselectivity providing differently substituted diarylflavone derivatives in good isolated yields (Table 5).

In summary, we have demonstrated the synthesis of a variety of arylated flavones via site-selective Suzuki–Miyaura reaction of 6,7-dibromoflavone. Numerous boronic acids reacted easily under mild conditions, providing different mono-/bis-/diarylated derivatives of flavone in moderate to excellent yields. In these reactions, the first attack occurred at the more electron-deficient carbon atom (C-7), providing 6-bromo-7-monoarylflavones in good yields. The Suzuki–Miyaura reaction of 6,7-dibromoflavone as a one-pot reaction was also studied, where the second bromide (C-6) also could take part in the coupling reaction. Moreover, the reaction of 6-bromo-7-monoarylflavones with different boronic acids did not show electronic effects of substituents on the boronic acid.

Table 5 Synthesis of **10a–e**[a]



6	R^1	Time (h)	6	R^2	10	Yield[b] (%) of 10
6i	4-CF_3	7.5	**6b**	3-MeO	**10a**	53
6i	4-CF_3	7.5	**6c**	4-MeO	**10b**	35
6n	4-Ph	5	**6c**	4-MeO	**10c**	57
6n	4-Ph	5	**6e**	4-F	**10d**	62
6n	4-Ph	5	**6i**	4-CF_3	**10e**	39

[a] Reaction conditions: (i) **5**, **6i** or **6n** (1.0 equiv), $Pd(PPh_3)_4$ (4 mol%), 2 M aq Cs_2CO_3 solution (3.0 equiv), 1,4-dioxane/MeOH (5:1), argon atmosphere, 75 °C, 5–7.5 h; (ii) **6b**, **6c**, **6e**, or **6i** (1.3 equiv), $Pd(PPh_3)_4$ (6 mol%), 100 °C, 2 h.
[b] Yields refer to pure isolated products.

All reactions were carried out in oven-dried pressure tubes under an argon atmosphere. Reagents were purchased from commercial sources (Sigma Aldrich, TCI, Alfa Aesar). Column chromatography was performed on silica gel (Merck 60, 0.043–0.06 mm). TLC was performed on Merck precoated aluminum plates (Si 60 F254). NMR spectra were recorded with Bruker Avance 250 II, Bruker Avance 300 III, Bruker 360 AM Avance, Bruker DRX 400, and Bruker Avance 500 spectrometers. ^{13}C and ^1H NMR spectra were referenced to signals of the deuterated solvents ($CHCl_3$, δ = 7.26 ^1H NMR; δ = 77.00 ^{13}C NMR). IR spectra were recorded with a Perkin–Elmer FT IR 1600 spectrophotometer (ATR) and with a Perkin-Elmer 16PC FT-IR spectrophotometer (KBr). The purity of the compounds was established by GC-MS (Agilent 7890, Agilent 5975 MS detector) with positive EI at 70 eV. HPLC-MS was performed using an Accela HPLC system (Thermo Electron Corp., San Jose, CA, USA). The LC system was coupled with a Thermo LTQ XL mass spectrometer (Thermo Electron Corp., San Jose, CA, USA) operated in a full scan positive ion ESI mode. The elementary analysis was carried out with an Elementar Vario Microtube instrument. Melting point data were determined by using Büchi B-540 equipment.

6,7-Dibromoflavone (5)

4′-Bromo-2′-hydroxyacetophenone (2)

Commercially available 3-bromophenol (**1**, 50 g, 0.289 mol) was added to a mixture of Ac_2O (187.5 mL, 1.987 mol) and anhyd NaOAc (50 g, 0.6095 mol) in a round-bottom flask. The mixture was refluxed and stirred for 2.5 h. The mixture was poured into ice-water (400 mL). The organic phase was separated, washed with water (200 mL) and sat. aq $NaHCO_3$ solution (100 mL). The combined aqueous phases were extracted with CH_2Cl_2 (3 × 80 mL), the combined organic phases were dried ($MgSO_4$), then filtered. The solvent was evaporated in vacuo to give the pure 3-bromophenyl acetate[17] (50.4 g, 81%) as pale yel-

low oil; R_f = 0.62 (toluene/EtOAc, 4:1). 3-Bromophenyl acetate was transferred into a three-neck flask and $AlCl_3$ (103 g, 0.7724 mol) was added in small portions. The mixture was heated and stirred at 170 °C for 3 h. The mixture was cooled to approx. 60 °C, and then ice (200 g) and 10% HCl solution (100 mL) were added and the mixture was stirred and distilled using steam. From the distillate white crystals were filtered off to give product **2**[19] (45 g, 90%); R_f = 0.55 (toluene); mp 39–40 °C.

Its spectral data are identical with the literature.[20]

IR (KBr): 3082, 3039, 3010, 1636, 1610, 1462, 1348, 1315, 1232, 1201, 967, 890, 735, 626, 497 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.61 (s, 3 H, Me), 7.04 (dd, *J* = 2.5, 8.5 Hz, 1 H, 5′-H), 7.18 (d, *J* = 2.5 Hz, 1 H, 3′-H), 7.58 (d, *J* = 8.5 Hz, 1 H, 6′-H), 12.34 (s, 1 H, OH).

4′,5′-Dibromo-2′-hydroxyacetophenone (3)

To a solution of 4′-bromo-2′-hydroxyacetophenone (**2**, 15 g, 69.75 mmol) in CS_2 (220 mL), cooled with an ice bath, was added anhyd $ZnCl_2$ (28.52 g, 209 mmol) with stirring. After 15 min Br_2 (3.8 mL, 74.17 mmol) was added, the temperature was allowed to warm up to r.t., and stirring was continued for 2 d. 5% aq $Na_2S_2O_3$ solution (200 mL) was poured into the mixture and the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and filtered. The solvent was evaporated in vacuo, and the solid residue was washed with *i*-Pr_2O (2 × 15 mL) and filtered to give product **3** (10.31 g, 48%) as off-white crystals; R_f = 0.58 (toluene); mp 131–133.3 °C.

IR (KBr): 3444, 3079, 3041, 3009, 1645, 1603, 1456, 1422, 1367, 1325, 1311, 1252, 1216, 967, 895, 785, 743, 635, 487 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.61 (s, 3 H, Me), 7.28 (s, 1 H, 3′-H), 7.91 (s, 1 H, 6′-H), 12.11 (s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 (C-2), 113.4 (C-5′), 120.1 (C-1′), 123.8 (C-3′), 133.1 (C-4′), 134.4 (C-6′), 161.2 (C-2′), 203.2 (C-1).

GC-MS: *m/z* (%) = 293.9 [M^+], 278.8 [M^+ – Me, 100], 250.8 [M^+ – Ac], 222.8, 142.9.

Anal. Calcd for $C_8H_6Br_2O_2$: C, 32.69; H, 2.06. Found: C, 32.75; H, 2.05.

4′,5′-Dibromo-2′-hydroxychalcone (4)

To the suspension of 4′,5′-dibromo-2′-hydroxyacetophenone (**3**, 10 g, 34.02 mmol) and EtOH (200 mL) was added 50% aq NaOH (7.12 mL, 136 mmol) to give a homogenous solution. To the solution benzaldehyde (3.8 mL, 37.42 mmol) was added and the mixture was stirred for 30 min and then it was allowed to stand at r.t. for 2 d. 10% HCl solution was added to reach pH 1; the precipitate was filtered off and washed with water (3 × 30 mL) to give **4** (12.790 g, 98%) as yellow crystals; R_f = 0.80 (toluene/EtOAc, 4:1); mp 144.4–145.8 °C.

IR (KBr): 3444, 3061, 3023, 2924, 1639, 1567, 1454, 1360, 1329, 1191, 1033, 729 cm^{-1}.

^1H NMR (360 MHz, 298 K, $CDCl_3$): δ = 7.37 (s, 1 H, 3′-H), 7.46–7.48 (m, 3 H, 3-H, 4-H, 5-H), 7.50–7.54 (d, *J* = 15.5 Hz, 1 H, β-H), 7.68–7.70 (m, 2 H, 2-H, 6-H), 7.95–7.99 (d, *J* =15.1 Hz, 1 H, α-H), 8.11 (s, 1 H, 6′-H), 12.75 (s, 1 H, OH).

^{13}C NMR (100 MHz, 298 K, $CDCl_3$): δ = 113.5 (C-5′), 119.1 (C-β), 120.5 (C-1′), 124.0 (C-3′), 129.1 (C-2, C-6), 129.3 (C-3, C-5), 131.6 (C-4), 133.0 (C-4′), 133.4 (C-6′), 134.2 (C-1), 147.2 (C-α), 162.4 (C-2′), 192.3 (C-γ).

GC-MS: *m/z* (%) = 380.9 [M^+, 100], 304.9 [M^+ – Br], 277.8, 249.8, 222.9, 165.1, 131.0, 104.1, 77.0.

Anal. Calcd for $C_{15}H_{10}Br_2O_2$: C, 47.16; H, 2.64. Found: C, 47.25; H, 2.67.

6,7-Dibromoflavone (5)

To the solution of 4′,5′-dibromo-2′-hydroxychalcone (**4**, 7.9 g, 20.678 mmol) in DMSO (120 mL), I_2 (315 mg, 1.24 mmol) was added and the mixture was moderately refluxed for 15 min. The mixture was poured into ice-water mixture (2 L), and then Na_2SO_3 was added and the mixture was stirred. The solid product **5** was filtered off as off-white crystals and washed with water (2 × 20 mL) and *i*-Pr_2O (2 × 15 mL); yield: 7.54 g (96%); R_f = 0.58 (toluene/EtOAc, 4:1); mp 230–231 °C.

IR (KBr): 3444, 3054, 3008, 1637, 1610, 1592, 1454, 1415, 1349, 911, 903, 769, 683 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 6.82 (s, 1 H, 3-H), 7.52–7.58 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.88–7.90 (d, *J* = 6.5 Hz, 2 H, 2′-H, 6′-H), 7.93 (s, 1 H, 8-H), 8.45 (s, 1 H, 5-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 107.8 (C-3), 121.8 (C-6), 123.6 (C-8), 124.3 (C-4a), 126.5 (C-2′, C-6′), 129.3 (C-3′, C-5′), 130.3 (C-4′), 130.6 (C-7), 131.2 (C-1′), 132.2 (C-5), 154.8 (C-8a), 163.9 (C-2), 176.6 (C-4).

GC-MS: *m/z* (%) = 379.9 [M^+, 100], 351.9, 277.8, 249.8, 163.0, 140.9, 102.0.

Anal. Calcd for $C_{15}H_8Br_2O_2$: C, 47.41; H, 2.12. Found: C, 47.36; H, 2.11.

Diarylation of 6,7-Dibromoflavone (5); General Procedure for 7a–i

To a mixture of 6,7-dibromoflavone (**5**, 95 mg, 0.25 mmol), 2 M aq Cs_2CO_3 solution (0.75 mmol), and boronic acid (0.58 mmol) in 1,4-dioxane/MeOH (5:1, 3.6 mL), in a pressure tube under argon, was added $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol). The mixture was stirred and heated at 100 °C in an aluminum heating block for the time given in Tables 2 and 3, until complete conversion. The mixture was dried ($MgSO_4$) and filtered off. The solvent was removed under reduced pressure; the residue was purified by column chromatography to give the pure cross-coupled product **7a–i**.

6,7-Diphenylflavone (7a)

Pale yellow crystals; yield: 63 mg (67%); mp 132–134 °C; R_f = 0.26 (heptane/EtOAc, 4:1).

IR (ATR): 3401, 3059, 3024, 2926, 1633, 1614, 1602, 1451, 1425, 1356, 777, 764, 695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.92 (s, 1 H, 3-H), 7.16–7.30 (m, 10 H, 2″-H, 3″-H, 4″-H, 5″-H, 6″-H, 1‴-H, 2‴-H, 3‴-H, 4‴-H, 5‴-H), 7.54–7.57 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.66 (s, 1 H, 8-H), 7.96–7.99 (dd, 2 H, 2′-H, 6′-H), 8.29 (s, 1 H, 8-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.8 (C-3), 119.8 (C-8), 122.8 (C-4a), 126.4 (C-2′, C-6′), 127.1, 127.4 (C-4″, C-4‴), 127.7 (C-4′), 128.1, 128.3 (C-2″,C-6″, C-2‴, C-6‴), 129.2 (C-3′, C-5′), 129.7, 130.0 (C-3″, C-5″, C-3‴, C-5‴), 131.8 (C-5), 131.9 (C-1′), 138.6 (C-6), 139.8, 139.9 (C-1″, C-1‴), 146.9 (C-7), 155.5 (C-8a), 163.8 (C-2), 178.4 (C-4).

Anal. Calcd for $C_{27}H_{18}O_2$: C, 86.61; H, 4.85. Found: C 86.50; H 4.79.

6,7-Bis(3-methoxyphenyl)flavone (7b)

Yellow crystals; yield: 81 mg (75%); mp 158–159 °C; R_f = 0.16 (heptane/EtOAc, 4:1).

IR (ATR): 3058, 2938, 2833, 1636, 1603, 1574, 1450, 1427, 1417, 1355, 1287, 1220, 1206, 1020, 770, 684 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (s, 3 H), 3.66 (s, 3 H) (3″-OMe, 3‴-OMe), 6.71–6.74 (m, 2 H, 4″-H, 4‴-H), 6.78–6.86 (m, 4 H, 2″-H, 6″-H, 2‴-H, 6‴-H), 6.93 (s, 1 H, 3-H), 7.14–7.24 (m, 2 H, 5″-H, 5‴-H), 7.53–7.57 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.68 (s, 1 H, 8-H), 7.96–7.99 (m, 2 H, 2′-H, 6′-H), 8.30 (s, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (C-3″-OMe, C-3‴-OMe), 107.8 (C-3), 113.4, 113.9 (C-4″, C-4‴), 115.0, 115.2 (C-2″, C-2‴), 119.7 (C-8), 122.1, 122.5 (C-6″, C-6‴), 122.9 (C-4a), 126.5 (C-2′, C-6′), 127.3 (C-4′), 129.2, 129.2 (C-5″, C-5‴), 129.4 (C-3′, C-5′), 131.84 (C-5), 131.87 (C-1′), 138.4 (C-6), 141.2, 141.2 (C-1″, C-1‴), 146.7 (C-7), 155.5 (C-8a), 159.4, 159.4 (C-3″, C-3‴), 163.8 (C-2), 178.3 (C-4).

Anal. Calcd for $C_{29}H_{22}O_4$: C, 80.17; H, 5.10. Found: C, 80.05; H, 5.11.

6,7-Bis(4-methoxyphenyl)flavone (7c)

Yellow crystals; yield: 76 mg (70%); mp 192–194 °C; R_f = 0.16 (heptane/EtOAc, 4:1).

IR (ATR): 3073, 3023, 2997, 2951, 2928, 2901, 2833, 1643, 1606, 1513, 1448, 1433, 1353, 1245, 1176, 1020, 829, 782, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 3.81 (s, 3 H) (4″-OMe, 4‴-OMe), 6.78–6.84 (m, 4 H, 3″-H, 5″-H, 3‴-H, 5‴-H), 6.91 (s, 1 H, 3-H), 7.09–7.16 (m, 4 H, 2″-H, 6″-H, 2‴-H, 6‴-H), 7.52–7.56 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.60 (s, 1 H, 8-H), 7.95–7.98 (m, 2 H, 2′-H, 6′-H), 8.22 (s, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3, 55.4 (C-4″-OMe, C-4‴-OMe), 107.7 (C-3), 113.7, 113.8 (C-2″, C-6″, C-2‴, C-6‴), 119.5 (C-8), 122.6 (C-4a), 126.4 (C-2′, C-6′), 127.2 (C-4′), 129.2 (C-3′, C-6′), 130.9, 131.1 (C-3″, C-5″, C-3‴, C-5‴), 131.7 (C-5), 132.0 (C-1′), 132.42, 132.44 (C-1″, C-1‴), 138.2 (C-6), 146.5 (C-7), 155.4 (C-8a), 158.8, 159.3 (C-4″, C-4‴), 163.6 (C-2), 178.4 (C-4).

Anal. Calcd for $C_{29}H_{22}O_4$: C, 80.17; H, 5.10. Found: C, 80.06; H, 5.07.

6,7-Bis(3-fluorophenyl)flavone (7d)

Pale yellow crystals; yield: 57 mg (56%); mp 177–179 °C; R_f = 0.30 (heptane/EtOAc, 4:1).

IR (ATR): 3063, 2918, 1641, 1622, 1611, 1606, 1578, 1575, 1359, 874, 837, 775, 687, 683 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86–7.05 (m, 7 H, 3-H, 2″-H, 5″-H, 6″-H, 2‴-H, 5‴-H, 6‴-H), 7.19–7.30 (m, 2 H, 4″-H, 4‴-H), 7.53–7.58 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.66 (s, 1 H, 8-H), 7.95–7.98 (m, 2 H, 2′-H, 6′-H), 8.27 (s, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.8 (C-3), 114.3–114.6, 114.9–115.1 (C-4″, C-4‴, J = 20.9 Hz), 116.49–116.76, 116.78–117.05 (C-2″, C-2‴, J = 20.7 Hz), 120.0 (C-8), 123.1 (C-4a), 125.48–125.52, 125.74–125.78 (C-6″, C-6‴, J = 3.0 Hz), 126.5 (C-2′, C-6′), 127.7 (C-4′), 129.3 (C-3′, C-5′), 129.8–129.9, 130.0–130.1 (C-5″, C-5‴, J = 8.4 Hz), 131.7 (C-1′), 132.0 (C-5), 137.21–137.23 (C-6, J = 2.0 Hz), 141.6, 141.7 (C-1″, C-1‴), 145.39–145.41 (C-7, J = 2.0 Hz), 155.7 (C-8a), 160.96–164.23, 161.02–164.29 (C-3″, C-3‴, J = 245.1 Hz), 164.1 (C-2), 178.1 (C-4).

Anal. Calcd for $C_{27}H_{16}F_2O_2$: C, 79.02; H, 3.93. Found: C, 78.94; H, 3.92.

6,7-Bis(4-fluorophenyl)flavone (7e)

Yellow crystals; yield: 60 mg (59%); mp 207–209 °C; R_f = 0.28 (heptane/EtOAc, 4:1).

IR (ATR): 3053, 2920, 1642, 1617, 1605, 1436, 1352, 1214, 909, 831, 771, 691 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.88 (s, 1 H, 3-H), 6.92–7.02 (m, 4 H, 3″-H, 5″-H, 3‴-H, 5‴-H), 7.09–7.19 (m, 4 H, 2″-H, 6″-H, 2‴-H, 6‴-H), 7.52–7.58 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.61 (s, 1 H, 8-H), 7.94–7.97 (m, 2 H, 2′-H, 6′-H), 8.22 (s, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.8 (C-3), 115.12–115.41, 115.32–115.61 (C-3″, C-5″, C-3‴, C-5‴, J = 21.3 Hz), 119.8 (C-8), 123.0 (C-4a), 126.4 (C-2′, C-6′), 127.4 (C-4), 129.2 (C-3′, C-5′), 131.33–131.43, 131.53–131.63 (C-2″, C-6″, C-2‴, C-6‴, J = 8.1 Hz), 131.8 (C-1′), 131.8 (C-5), 135.61–135.65, 135.66–135.71 (C-1″, C-1‴, J = 3.6 Hz), 137.3 (C-6), 145.6 (C-7), 155.5 (C-8a), 160.5–163.8, 160.8–164.1 (C-4″, C-4‴, J = 246.0 Hz), 163.7 (C-2), 178.1 (C-4).

GC-MS: m/z (%) = 410.1 [M$^+$, 100], 306.9, 280.0, 251.0, 207.0, 102.0.

Anal. Calcd for $C_{27}H_{16}F_2O_2$: C, 79.02; H, 3.93. Found: C, 79.10; H, 3.89.

6,7-Bis(3-chlorophenyl)flavone (7f)

Yellow crystals; yield: 74 mg (66%); mp 161.5–163.7 °C; R_f = 0.27 (heptane/EtOAc, 4:1).

IR (ATR): 3444, 3061, 1649, 1620, 1449, 1356, 788, 774, 687 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.89 (s, 1 H, 3-H), 6.96–7.02 (m, 2 H, 4″-H, 4‴-H), 7.16–7.30 (m, 6 H, 2″-H, 5″-H, 6″-H, 2‴-H, 5‴-H, 6‴-H), 7.54–7.57 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.63 (s, 1 H, 8-H), 7.94–7.97 (m, 2 H, 2′-H, 6′-H), 8.24 (s, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.8 (C-3), 120.0 (C-8), 123.2 (C-4a), 126.4 (C-2′, C-6′), 127.5, 127.6 (C-4″, C-4‴), 128.0, 128.1 (C-2″, C-2‴), 128.2 (C-4′), 129.2 (C-3′, C-5′), 129.4, 129.5 (C-5″, C-5‴), 129.6, 129.9 (C-6″, C-6‴), 131.6 (C-1′), 131.9 (C-5), 134.2, 134.4 (C-3″, C-3‴), 136.8 (C-6), 141.1, 141.2 (C-1″, C-1‴), 145.0 (C-7), 155.6 (C-8a), 163.8 (C-2), 177.9 (C-4).

Anal. Calcd for $C_{27}H_{16}Cl_2O_2$: C, 73.15; H, 3.64. Found: C, 73.10; H, 3.61.

6,7-Bis(4-chlorophenyl)flavone (7g)

Yellow crystals; yield: 100 mg (90%); mp 222–224 °C; R_f = 0.27 (heptane/EtOAc, 4:1).

IR (ATR): 3056, 2919, 1634, 1616, 1448, 1434, 1355, 1088, 1010, 834, 765, 733, 682 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (s, 1 H, 3-H), 7.07–7.14 (m, 4 H, 3″-H, 5″-H, 3‴-H, 5‴-H), 7.23–7.30 (m, 4 H, 2″-H, 6″-H, 2‴-H, 6‴-H), 7.54–7.58 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.62 (s, 1 H, 5-H), 7.94–7.98 (m, 2 H, 2′-H, 6′-H), 8.24 (s, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.8 (C-3), 119.9 (C-8), 123.0 (C-4a), 126.5 (C-2′, C-6′), 127.6 (C-4′), 128.6, 128.8 (C-2″, C-6″, C-2‴, C-6‴), 129.3 (C-3″, C-5″), 131.0, 131.3 (C-3″, C-5″, C-3‴, C-5‴), 131.7 (C-1′), 132.1 (C-5), 133.6, 134.3 (C-4″, C-4‴), 137.2 (C-6), 137.96, 138.01 (C-1″,C-1‴), 145.5 (C-7), 155.7 (C-8a), 164.1 (C-2), 178.2 (C-4).

Anal. Calcd for $C_{27}H_{16}Cl_2O_2$: C, 73.15; H, 3.64. Found: C, 73.08; H, 3.63.

6,7-Bis[3-(trifluoromethyl)phenyl]flavone (7h)

Pale yellow crystals; yield: 92 mg (72%); mp 185–187 °C; R_f = 0.30 (heptane/EtOAc, 4:1).

IR (ATR): 3065, 3044, 1643, 1622, 1327, 1155, 1118, 1096, 1074, 807, 768, 708, 703, 679, 653 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.93 (s, 1 H, 3-H), 7.32–7.45 (m, 6 H, 2″-H, 5″-H, 6″-H, 2‴-H, 5‴-H, 6‴-H), 7.51–7.57 (m, 5 H, 3′-H, 4′-H, 5′-H, 2″-H, 2‴-H), 7.71 (s, 1 H, 8-H), 7.96–7.99 (m, 2 H, 2′-H, 6′-H), 8.32 (s, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.0 (C-3), 120.1 (C-8), 122.0–125.7, 122.1–125.7 (C-3″-CF_3, C-3‴-CF_3, *J* = 270.8 Hz), 123.6 (C-4a), 124.22–124.27, 124.77–124.82 (C-4″, C-4‴), 126.5 (C-2′, C-6′), 126.87, 126.92 (C-2″, C-2‴), 127.7 (C-4′), 128.9, 129.1 (C-5″, C-5‴), 129.3 (C-3′, C-5′), 130.67–131.10, 130.89–131.32 (C-3″, C-3‴, *J* = 32.3 Hz), 131.6 (C-1′), 132.1 (C-5), 133.0, 133.3 (C-6″, C-6‴), 136.9 (C-6), 139.98, 140.05 (C-1″, C-1‴), 145.1 (C-7), 155.9 (C-8a), 164.1 (C-2), 178.0 (C-4).

Anal. Calcd for $C_{29}H_{16}F_6O_2$: C, 68.24; H, 3.16. Found: C, 68.16; H, 3.15.

6,7-Bis[4-(trifluoromethyl)phenyl]flavone (7i)

The crude product was purified by washing with *i*-Pr_2O (2 × 3 mL); orange crystals; yield: 97 mg (76%); mp 208–209 °C.

IR (ATR): 3066, 2919, 2848, 1645, 1617, 1608, 1436, 1405, 1324, 1158, 1106, 1066, 839, 774, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.88 (s, 1 H, 3-H), 7.26–7.33 (m, 4 H, 2″-H, 6″-H, 2‴-H, 6‴-H), 7.51–7.58 (m, 7 H, 3′-H, 4′-H, 5′-H, 3″-H, 5″-H, 3‴-H, 5‴-H), 7.66 (s, 1 H, 8-H), 7.93–7.96 (dd, 2 H, 2″-H, 6″-H), 8.27 (s, 1 H, 5-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 108.0 (C-3), 120.3 (C-8), 122.5, 122.6 (C-4″-CF_3, C-4‴-CF_3), 123.6 (C-4a), 125.36–125.39, 125.53–125.55 (C-3″, C-5″, C-3‴, C-5‴, *J* = 3.6 Hz), 126.4 (C-2′, C-6′), 128.0 (C-4′), 129.3 (C-3′, C-5′), 129.5–129.9 (C-4″, C-4‴, *J* = 32.7 Hz), 130.1, 130.3 (C-2″, C-6″, C-2‴, C-6‴), 131.6 (C-1′), 132.0 (C-5), 136.8 (C-6), 143.0 (C-1″, C-1‴), 145.0 (C-7), 155.8 (C-8a), 163.9 (C-2), 177.8 (C-4).

Anal. Calcd for $C_{29}H_{16}F_6O_2$: C, 68.24; H, 3.16. Found: C, 70.27; H, 3.15.

7-(2,6-Dimethylphenyl)flavone (8a)

Pale yellow crystals; yield: 32 mg (39%); mp 194–194 °C; R_f = 0.37 (heptane/EtOAc, 8:1).

IR (ATR): 3051, 3022, 2951, 2919, 1636, 1607, 1418, 828, 771, 761, 677 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 6 H, 2″-Me, 6″-Me), 6.91 (s, 1 H, 3-H), 7.14–7.26 (m, 4 H, 6-H, 3″-H, 4″-H, 5″-H), 7.420–7.424 (d, *J* = 1.2 Hz, 1 H, 8-H), 7.52–7.57 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.94–7.97 (m, 2 H, 2′-H, 6′-H), 8.30–8.33 (d, *J* = 8.1 Hz, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (C-2″-Me, C-6″-Me), 107.8 (C-3), 118.5 (C-8), 122.7 (C-4a), 126.0 (C-6), 126.4 (C-2′, C-6′), 126.8 (C-4″), 127.7 (C-3″, C-5″), 127.9 (C-4′), 129.2 (C-3′, C-5′), 131.7 (C-5), 131.9 (C-1′), 135.6 (C-2″, C-6″), 140.0 (C-1″), 147.8 (C-7), 156.6 (C-8a), 163.6 (C-2), 178.4 (C-4).

Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.65; H, 5.52.

7-(2,4,6-Trimethylphenyl)flavone (8b)

Yellow crystals; yield: 36 mg (43%); mp 219–221 °C; R_f = 0.32 (heptane/EtOAc, 8:1).

IR (ATR): 3060, 3026, 2914, 2854, 1635, 1622, 1610, 1418, 1367, 833, 772, 764, 683 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.05 (s, 6 H, 2″-Me, 6″-Me), 2.37 (s, 3 H, 4″-Me), 6.91 (s, 1 H, 3-H), 6.99 (s, 2 H, 3″-H, 5″-H), 7.22–7.25 (dd, 1 H, 6-H), 7.40–7.41 (d, *J* = 1.3 Hz, 1 H, 8-H), 7.52–7.57 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.94–7.97 (m, 2 H, 2′-H, 6′-H), 8.28–8.31 (d, *J* = 8.0 Hz, 1 H, 5-H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 20.7 (C-2″-Me, C-6″-Me), 21.2 (C-4″-Me), 107.8 (C-3), 118.7 (C-8), 122.6 (C-4a), 125.9 (C-6), 126.4 (C-2′, C-6′), 127.2 (C-4′), 128.4 (C-3″, C-5″), 129.2 (C-3′, C-5′), 131.7 (C-5), 131.9 (C-1′), 135.5 (C-1″), 137.2 (C-4″), 137.6 (C-2″, C-6″), 147.9 (C-7), 156.5 (C-8a), 163.6 (C-2), 178.4 (C-4).

LC-MS: *m*/*z* = 341.4 [M + H$^+$].

Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.59; H, 5.94.

Monoarylation of 6,7-Dibromoflavone (5); General Procedure for 9a–e

To a mixture of 6,7-dibromoflavone (**5**, 95 mg, 0.25 mmol), 2 M aq Cs_2CO_3 solution (0.75 mmol), and boronic acid (0.25 mmol) in 1,4-dioxane/MeOH (5:1, 6 mL), in a pressure tube under argon, was added $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol). The mixture was stirred and heated at 70 °C in an aluminum heating block for the time given in Table 4, until full conversion. The mixture was dried ($MgSO_4$) and filtered off. The solvent was removed under reduced pressure; the residue was purified by column chromatography to give the pure monosubstituted product **9a–e**.

6-Bromo-7-(4-fluorophenyl)flavone (9a)

White crystals; yield: 53 mg (53%); mp 206–208 °C; R_f = 0.32 (hexane/CH_2Cl_2/EtOAc, 7:4:1).

IR (KBr): 3444, 3042, 1645, 1618, 1604, 1517, 1450, 1423, 1396, 1359, 1227, 915, 835, 769, 686 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.83 (s, 1 H, 3-H), 7.15–7.19 (t, 2 H, 3″-H, 5″-H), 7.43–7.54 (m, 6 H, 8-H, 3′-H, 4′-H, 5′-H, 2″-H, 6″-H), 7.89–7.91 (d, *J* = 5.4 Hz, 2 H, 2′-H, 6′-H), 8.48 (s, 1 H, 5-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 107.7 (C-3), 115.3–115.6 (C-3″, C-5″, *J* = 21.6 Hz), 119.4 (C-6), 120.7 (C-8), 124.2 (C-4a), 126.4 (C-2′, C-6′), 129.2 (C-3′, C-5′), 130.1 (C-4′), 131.1–131.2 (C-2″, C-6″, *J* = 8.3 Hz), 131.5 (C-1′), 132.0 (C-5), 135.5 (C-1″), 147.1 (C-7), 155.0 (C-8a), 161.6–164.3 (C-4″, *J* = 247.2 Hz), 163.9 (C-2), 176.9 (C-4).

GC-MS: *m*/*z* (%) = 394.0 [M$^+$], 368.0, 291.9, 257.0, 207.0, 182.9, 157.0 [100], 128.7, 102.0, 76.0.

Anal. Calcd for $C_{21}H_{12}BrFO_2$: C, 63.82; H, 3.06. Found: C, 63.76; H, 3.03.

6-Bromo-7-[4-(trifluoromethyl)phenyl]flavone (9b)

White crystals; yield: 42 mg (38%); mp 230–232 °C; R_f = 0.40 (heptane/EtOAc, 6:1).

IR (ATR): 3072, 3051, 2922, 1646, 1614, 1603, 1419, 1396, 1323, 1164, 1159, 1119, 1108, 1072, 1058, 1016, 910, 833, 771, 682, 625, 617 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.85 (s, 1 H, 3-H), 7.52–7.61 (m, 6 H, 8-H, 3′-H, 4′-H, 5′-H, 2″-H, 6″-H), 7.74–7.76 (d, *J* = 8.3 Hz, 2 H, 3″-H, 5″-H), 7.88–7.91 (m, 2 H, 2′-H, 6′-H), 8.50 (s, 1 H, 5-H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 107.8 (C-3), 118.9 (C-6), 120.8 (C-8), 124.6 (C-4a), 121.9–126.3 (C-CF_3, *J* = 272.7 Hz), 125.3–125.5 (C-3″, C-5″), 126.4 (C-2′, C-6′), 129.3 (C-3′, C-5′), 129.8 (C-2″, C-6″), 130.3 (C-4′), 130.6–131.1 (C-4″, *J* = 32.8 Hz), 131.4 (C-1′), 132.1 (C-5), 143.0 (C-1″), 146.6 (C-7), 155.0 (C-8a), 164.1 (C-2), 176.8 (C-4).

Anal. Calcd for $C_{22}H_{12}BrF_3O_2$: C, 59.35; H, 2.72. Found: C, 59.26; H, 2.75.

6-Bromo-7-(4-methylphenyl)flavone (9c)

White crystals; yield: 56 mg (57%); mp 174–176 °C; R_f = 0.38 (heptane/CH_2Cl_2/EtOAc, 10:5:1).

IR (ATR): 3033, 2917, 1643, 1599, 1417, 1394, 1357, 814, 764, 682, 621 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, Me), 6.80 (s, 1 H, 3-H), 7.19–7.23 (q, 4 H, 2″-H, 3″-H, 5″-H, 6″-H), 7.46–7.49 (m, 4 H, 8-H, 3′-H, 4′-H, 5′-H), 7.83–7.86 (dd, 2 H, 2′-H, 6′-H), 8.44 (s, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (C-Me), 107.7 (C-3), 119.7 (C-6), 120.7 (C-8), 123.9 (C-4a), 126.5 (C-2′, C-6′), 129.1 (C-2″, C-6″), 129.2 (C-3′, C-5′), 129.3 (C-3″, C-5″), 130.1 (C-4′), 131.6 (C-1′), 132.0 (C-5), 136.8 (C-4″), 138.7 (C-1″), 148.3 (C-7), 155.1 (C-8a), 164.0 (C-2), 177.2 (C-4).

LC-MS: *m*/*z* = 393.0 [M + H$^+$].

Anal. Calcd for $C_{22}H_{15}BrO_2$: C, 67.53; H, 3.86. Found: C, 67.44; H, 3.82.

6-Bromo-7-(4-*tert*-butylphenyl)flavone (9d)

White crystals; yield: 57 mg (49%); mp 216–219 °C; R_f = 0.24 (heptane/CH_2Cl_2/EtOAc, 10:5:1).

IR (KBr): 3444, 3064, 2961, 1649, 1619, 1604, 1450, 1416, 1395, 1358, 835, 774, 687 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, *t*-Bu), 6.83 (s, 1 H, 3-H), 7.41–7.43 (d, *J* = 8.1 Hz, 2 H, 2″-H, 6″-H), 7.48–7.55 (m, 6 H, 8-H, 3′-H, 4′-H, 5′-H, 3″-H, 5″-H), 7.88–7.90 (d, *J* = 7.6 Hz, 2 H, 2′-H, 6′-H), 8.49 (s, 1 H, 5-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 31.4 [C(CH_3)$_3$], 34.8 [C(CH$_3$)$_3$], 107.7 (C-3), 119.5 (C-6), 120.7 (C-8), 123.9 (C-4a), 125.3 (C-3″, C-5″), 126.4 (C-2″, C-6″), 129.0 (C-2′, C-6′), 129.2 (C-3′, C-5′), 130.0 (C-4′), 131.6 (C-1′), 131.9 (C-5), 136.6 (C-1″), 148.2 (C-7), 151.8 (C-4″), 155.1 (C-8a), 163.8 (C-2), 177.1 (C-4).

Anal. Calcd for $C_{25}H_{21}BrO_2$:C, 69.29; H, 4.88. Found: C, 69.34; H, 4.79.

7-(Biphenyl-4-yl)-6-bromoflavone (9e)

Pale yellow crystals; yield: 67 mg (59%); mp 227–228 °C; R_f = 0.30 (heptane/CH_2Cl_2/EtOAc, 12:4:1).

IR (KBr): 3444, 3066, 3031, 1652, 1619, 1448, 1415, 1396, 1355, 768, 687 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.85 (s, 1 H, 3-H), 7.36–7.40 (m, 1 H, 4‴-H), 7.45–7.56 (m, 7 H, 3′-H, 4′-H, 5′-H, 2″-H, 3″-H, 5″-H, 6″-H), 7.60 (s, 1 H, 8-H), 7.65–7.72 (m, 4 H, 2‴-H, 3‴-H, 5‴-H, 6‴-H), 7.89–7.92 (d, *J* = 7.6 Hz, 2 H, 2′-H, 6′-H), 8.52 (s, 1 H, 5-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 107.8 (C-3), 119.4 (C-6), 120.7 (C-8), 124.1 (C-4a), 126.4 (C-2″, C-6″), 127.0 (C-3″, C-5″), 127.3 (C-2‴, C-6‴), 127.8 (C-4‴), 129.0 (C-2′, C-6′), 129.2 (C-3′, C-5′), 129.8 (C-3‴, C-5‴), 130.2 (C-4′), 131.5 (C-1′), 132.0 (C-5), 138.5 (C-1″), 140.4 (C-4″), 141.5 (C-1‴), 147.8 (C-7), 155.1 (C-8a), 163.9 (C-2), 177.0 (C-4).

Anal. Calcd for $C_{27}H_{17}BrO_2$: C, 71.54; H, 3.78. Found: C, 71.58; H, 3.81.

Diarylation of 6,7-Dibromoflavone (5) with Different Boronic Acids; General Procedure for Differently Substituted 6,7-Diarylflavone Derivatives 10a–e

To a mixture of 6,7-dibromoflavone (**5**, 190 mg, 0.50 mmol), 2 M aq Cs_2CO_3 solution (1.50 mmol), and boronic acid (0.50 mmol) in 1,4-dioxane/MeOH (5:1, 6 mL), in a pressure tube under argon, was added $Pd(PPh_3)_4$ (22 mg, 0.02 mmol). The mixture was stirred and heated at 75 °C in an aluminum heating block for the times given in Table 5, until full conversion of the 6,7-dibromoflavone (**5**). Further $Pd(PPh_3)_4$ (34 mg, 0.03 mmol) and the other boronic acid (0.65 mmol) were added. The mixture was stirred and heated at 100 °C for the times given in Table 5, until full conversion of the monocoupled product. The mixture was dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure; the residue was purified by column chromatography to give the differently substituted diarylflavones **10a–e**.

6-(3-Methoxyphenyl)-7-[4-(trifluoromethyl)phenyl]flavone (10a)

White crystals; yield: 130 mg (53%); mp 200–201 °C; R_f = 0.29 (heptane/CH_2Cl_2/EtOAc, 9:4:1).

IR (ATR): 3066, 2945, 2928, 2904, 2831, 1643, 1607, 1446, 1323, 1209, 1127, 1107, 1067, 1016, 837, 779, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.68 (s, 3 H, OMe), 6.70–6.71 (m, 1 H, 2″-H), 6.73–6.76 (m, 1 H, 4″-H), 6.81–6.85 (m, 1 H, 6″-H), 6.95 (s, 1 H, 3-H), 7.16–7.21 (t, 1 H, 5″-H), 7.36–7.39 (d, *J* = 8.1 Hz, 2 H, 2‴-H, 6‴-H), 7.55–7.61 (m, 5 H, 3′-H, 4′-H, 5′-H, 3‴-H, 5‴-H), 7.68 (s, 1 H, 8-H), 7.97–8.01 (m, 2 H, 2′-H, 6′-H), 8.34 (s, 1 H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (C-OMe), 107.9 (C-3), 113.6 (C-4″), 115.4 (C-2″), 119.9 (C-8), 122.4–126.0 (C-CF_3, *J* = 270.5 Hz), 122.6 (C-6″), 123.3 (C-4a), 125.2–125.4 (C-3‴, C-5‴), 126.5 (C-2′, C-6′), 127.7 (C-4′), 129.3 (C-3′, C-5′), 129.4 (C-5″), 129.7–130.1 (C-4‴, *J* = 32.3 Hz), 130.0 (C-2‴, C-6‴), 131.7 (C-1′), 132.0 (C-5), 138.4 (C-6), 140.5 (C-1″), 143.7 (C-1‴), 145.2 (C-7), 155.5 (C-8a), 159.5 (C-3″), 164.0 (C-2), 178.2 (C-4).

GC-MS: *m*/*z* (%) = 372.1 [M$^+$, 100], 429.1, 403.1, 370.0, 342.0, 283.1, 250.9, 202.0, 102.1.

Anal. Calcd for $C_{29}H_{19}F_3O_3$: C, 73.72; H, 4.05. Found: C, 73.65; H, 4.01.

6-(4-Methoxyphenyl)-7-[4-(trifluoromethyl)phenyl]flavone (10b)

Yellow crystals; yield: 85 mg (35%); mp 193–195 °C; R_f = 0.16 (heptane/EtOAc, 6:1).

IR (ATR): 3062, 3017, 2957, 2937, 2900, 2836, 1643, 1606, 1433, 1246, 1127, 1107, 1068, 843, 830, 780, 692 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OMe), 6.80–6.82 (m, 2 H, 3″-H, 5″-H), 6.98 (s, 1 H, 3-H), 7.07–7.09 (m, 2 H, 2″-H, 6″-H), 7.36–7.37 (d, *J* = 8.0 Hz, 2 H, 2‴-H, 6‴-H), 7.57–7.60 (m, 5 H, 3′-H, 4′-H, 5′-H, 6‴-H, 5‴-H), 7.66 (s, 1 H, 8-H), 7.98–8.00 (dd, 2 H, 2′-H, 6′-H), 8.29 (s, 1 H, 5-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.4 (C-OMe), 107.8 (C-3), 113.9 (C-3″, C-5″), 119.9 (C-8), 123.1–125.3 (C-CF_3, *J* = 270.5 Hz), 123.3 (C-4a), 125.3–125.4 (C-3‴, C-5‴), 126.5 (C-2′, C-6′), 127.5 (C-4′), 129.3 (C-3′, C-5′), 129.7–130.0 (C-4‴, *J* = 32.5 Hz), 130.1 (C-2‴, C-6‴), 131.2 (C-2″, C-6″), 131.5 (C-1′), 131.8 (C-1″), 132.0 (C-5), 138.3 (C-6), 143.8 (C-1‴), 145.2 (C-7), 155.3 (C-8a), 159.1 (C-4″), 164.0 (C-2), 178.2 (C-4).

Anal. Calcd for $C_{29}H_{19}F_3O_3$: C, 73.72; H, 4.05. Found: C, 73.75; H, 4.07.

7-(Biphenyl-4-yl)-6-(4-methoxyphenyl)flavone (10c)

Pale yellow crystals; yield: 137 mg (57%); mp 204–206 °C; R_f = 0.33 (hexane/CH_2Cl_2/EtOAc, 9:4:2).

IR (KBr): 3444, 3051, 3030, 1647, 1619, 1608, 1450, 1433, 1357, 1249, 1177, 835, 771 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.76 (s, 3 H, OMe), 6.76–6.78 (d, *J* = 7.9 Hz, 2 H, 3″-H, 5″-H), 6.85 (s, 1 H, 3-H), 7.10–7.12 (d, *J* = 7.6 Hz, 2 H, 2″-H, 6″-H), 7.26–7.28 (d, *J* = 7.6 Hz, 2 H, 2‴-H, 6‴-H), 7.31–7.35 (m, 1 H, 4⁗-H), 7.40–7.44 (m, 2 H, 3⁗-H, 5⁗-H), 7.51–7.56 (m, 5 H, 3′-H, 4′-H, 5′-H, 2⁗-H, 6⁗-H), 7.58–7.60 (d, *J* = 7.6 Hz, 2 H, 3‴-H, 5‴-H), 7.63 (s, 1 H, 8-H), 7.92–7.94 (d, *J* = 7.2 Hz, 2 H, 2′-H, 6′-H), 8.24 (s, 1 H, 5-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 55.3 (C-OMe), 107.7 (C-3), 113.7 (C-3″, C-5″), 119.7 (C-8), 122.9 (C-4a), 126.4 (C-2′, C-6′), 126.9 (C-3‴, C-5‴), 127.1 (C-2‴, C-6‴), 127.2 (C-4⁗), 127.6 (C-2⁗, C-6⁗), 128.9 (C-3′, C-5′), 129.2 (C-3⁗, C-5⁗), 130.1 (C-4′), 131.2 (C-2″, C-6″), 131.7 (C-5), 131.9 (C-6), 132.2 (C-1′), 138.1 (C-1″), 139.0 (C-4‴), 140.3 (C-1⁗), 140.4 (C-1‴), 146.2 (C-7), 155.3 (C-8a), 158.8 (C-4″), 163.5 (C-2), 178.3 (C-4).

Anal. Calcd for $C_{34}H_{24}O_3$: C, 84.98; H, 5.03. Found: C, 85.03; H, 5.01.

7-(Biphenyl-4-yl)-6-(4-fluorophenyl)flavone (10d)

White crystals; yield: 145 mg (62%); mp 212–214 °C; R_f = 0.29 (hexane/CH_2Cl_2/EtOAc, 9:4:2).

IR (KBr): 3445, 3056, 3030, 1647, 1920, 1606, 1451, 1435, 1357, 838, 818 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 6.86 (s, 1 H, 3-H), 6.91–6.96 (m, 2 H, 3″-H, 5″-H), 7.14–7.17 (m, 2 H, 2″-H, 6″-H), 7.23–7.26 (d, *J* = 7.9 Hz, 2 H, 2‴-H, 6‴-H), 7.32–7.36 (m, 1 H, 4⁗-H), 7.41–7.45 (m, 2 H, 3⁗-H, 5⁗-H), 7.51–7.53 (m, 5 H, 3′-H, 4′-H, 5′-H, 2⁗-H, 6⁗-H), 7.58–7.60 (d, *J* = 7.6 Hz, 2 H, 3‴-H, 5‴-H), 7.66 (s, 1 H, 8-H), 7.93–7.95 (d, *J* = 7.2 Hz, 2 H, 2′-H, 6′-H), 8.23 (s, 1 H, 5-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 107.8 (C-3), 115.1–115.4 (C-3″, C-5″, *J* = 21.4 Hz), 119.8 (C-8), 123.0 (C-4a), 126.4 (C-2′, C-6′), 127.0 (C-3‴, C-5‴), 127.1 (C-2‴, C-6‴), 127.4 (C-4⁗), 127.7 (C-2⁗, C-6⁗), 129.0 (C-3′, C-5′), 129.2 (C-3⁗, C-5⁗), 130.2 (C-4′), 131.6–131.7 (C-2″, C-6″, *J* = 7.7 Hz), 131.8 (C-5), 131.8 (C-1′), 135.9 (C-1″), 137.4 (C-6), 138.6 (C-4‴), 140.1 (C-1⁗), 140.4 (C-1‴), 146.3 (C-7), 155.5 (C-8a), 160.8–163.5 (C-4″, *J* = 245.4 Hz), 163.7 (C-2), 178.2 (C-4).

LC-MS: *m*/*z* = 469.3 [M + H^+].

Anal. Calcd for $C_{33}H_{21}FO_2$: C, 84.60; H, 4.52. Found: C, 84.64; H, 4.49.

7-(Biphenyl-4-yl)-6-[4-(trifluoromethyl)phenyl]flavone (10e)

Yellow crystals; yield: 97 mg (39%); mp 206–208 °C; R_f = 0.33 (hexane/CH_2Cl_2/EtOAc, 7:5:1).

IR (KBr): 3445, 3059, 3031, 1645, 1620, 1451, 1436, 1357, 1325, 1166, 1124, 1069, 843, 771 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 6.89 (s, 1 H, 3-H), 7.24–7.26 (d, *J* = 7.9 Hz, 2 H, 2‴-H, 6‴-H), 7.33–7.38 (m, 3 H, 3″-H, 5″-H, 4⁗-H), 7.43–7.47 (m, 2 H, 3⁗-H, 5⁗-H), 7.56–7.61 (m, 7 H, 3′-H, 4′-H, 5′-H, 2″-H, 6″-H, 2⁗-H, 6⁗-H), 7.59–7.61 (d, *J* = 7.6 Hz, 2 H, 3‴-H, 5‴-H), 7.71 (s, 1 H, 8-H), 7.95–7.97 (m, 2 H, 2′-H, 6′-H), 8.28 (s, 1 H, 5-H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 107.9 (C-3), 120.1 (C-8), 122.8–125.8 (CF_3, *J* = 270.1 Hz), 123.1 (C-4a), 125.2 (C-3″, C-5″), 126.5 (C-2′, C-6′), 127.2 (C-2‴, C-3‴, C-5‴, C-6‴), 127.8 (C-2⁗, C-4⁗, C-6⁗), 129.0 (C-2″, C-6″), 129.3 (C-3′, C-5′), 129.6 (C-4″), 130.2 (C-4′), 130.4 (C-3⁗, C-5⁗), 131.8 (C-1′), 131.9 (C-5), 136.9 (C-6), 138.2 (C-4‴), 140.2 (C-1⁗), 140.8 (C-1‴), 143.6 (C-1″), 146.3 (C-7), 155.9 (C-8a), 163.8 (C-2), 178.1 (C-4).

Anal. Calcd for $C_{34}H_{21}F_3O_2$: C, 78.75; H, 4.08. Found: C, 78.80; H, 4.06.

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Supporting Information

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