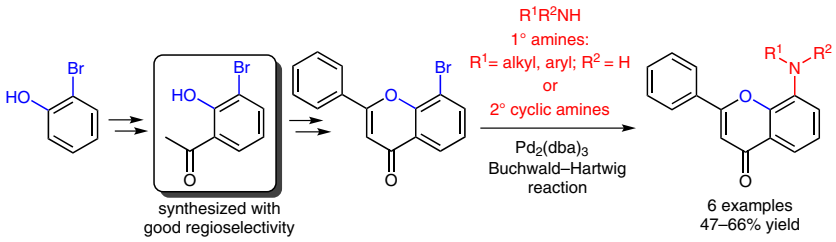
Synthesis D. Pajtás et al. Paper

Synthesis of 8-Bromoflavone and Its Buchwald–Hartwig Reaction with Amines

Dávid Pajtás
Tamás Patonay †
Krisztina Kónya*

Department of Organic Chemistry, University of Debrecen, Egyetem tér 1, 4032 Debrecen, Hungary
konya.krisztina@science.unideb.hu

Dedicated to the memory of Prof. Tamás Patonay



Received: 29.07.2015
Accepted: 27.08.2015
Published online: 30.09.2015
DOI: 10.1055/s-0035-1560325; Art ID: ss-2015-t0461-op

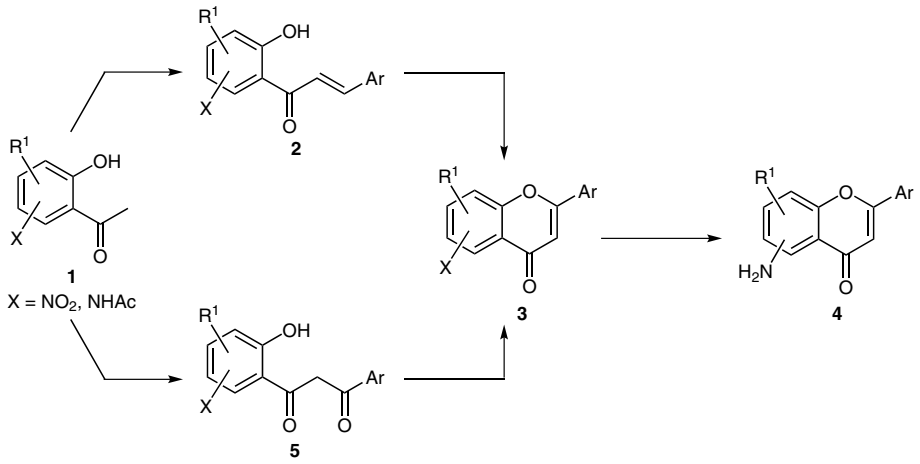
Abstract Simple and convenient synthesis of 8-bromoflavone was achieved, starting from 2-bromophenol through 3′-bromo-2′-hydroxyacetophenone whose preparation was managed to be solved by optimized Fries rearrangement. The Buchwald–Hartwig reaction of 8-bromoflavone with different type of primary and secondary amines was carried out.

Key words palladium, Buchwald–Hartwig reaction, flavones, catalysis, Fries rearrangement

Flavones (2-aryl-4*H*-1-benzopyran-4-ones) are widespread in nature mostly as plant metabolites.[1] In addition to their frequent occurrence, flavones also show versatile biological activities, for example, antioxidant, anti-inflammatory, and antimicrobial properties.[2] Notably, many aminoflavone derivatives have considerable enzyme inhibitory effects, such as α-glucosidase,[2d] tyrosine kinase,[3] cyclin-dependent kinase[4] inhibitors; in addition, antiproliferative,[5] antitumor,[6] cytotoxic effect,[7] and central nervous system protective properties[8] have also been observed.

Most syntheses of flavones are based on the corresponding chromone (4*H*-1-benzopyran-4-one) core structure by conventional methods. However, synthesis of aminoflavones suffer from limitations, especially in the case of derivatives linked to their amine substituents at ring A. The most common synthetic methods are based on Baker–Venkataraman rearrangement[9,10] or Claisen–Schmidt condensation[11,12] (Scheme 1).

The main problems of these methods are the synthesis of the corresponding acetophenone **1**, which is limited by the regioselectivity of the nitration of acetophenone and/or the sensitivity of the R^1 substituents under the harsh conditions of nitration. An alternative way is the nitration and re-



Scheme 1 Synthesis of aminoflavone derivatives by conventional methods

duction of previously prepared flavone moiety, but these possibilities are also limited by the regioselectivity and reactivity patterns of the nitration step.[3b,8,13]

Synthesizing derivatives with alkyl-/arylamino or disubstituted amino function represents a much greater challenge than the formation of the amino group. Due to the lack of selectivity, direct alkylation leads to low yields.[5,12g]

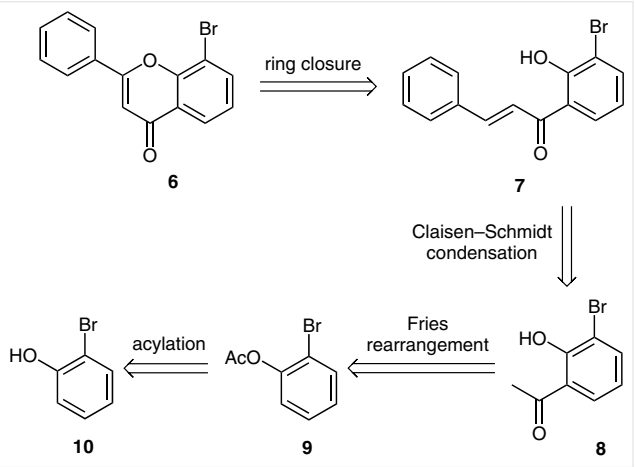
Over the last few decades, Buchwald–Hartwig amination of halo-substituted aromatic/heteroaromatic systems became a useful method for synthesizing alkyl- and arylamino-substituted arenes.[14] Nevertheless, in the field of aminoflavone derivatives only sporadic examples have been published. The synthesis of 4′-aminoisoflavone started from its bromide,[7] while 7-amino-5-hydroxyflavone was prepared from the corresponding triflate.[15] Caddick et al.[16] used Buchwald–Hartwig reaction for the amination of bromo- or triflyloxy-substituted flavones under microwave activation but only hexylamine was used as the nitrogen source.

Previously our group published the results of the amination of 6- and 7-bromoflavone with different types of primary, secondary amines, and aniline derivatives.[17] Although Caddick et al.[16] mention the Buchwald–Hartwig amination of 8-bromoflavone (**6**) with hexylamine, no other example was presented. Moreover, to the best of our knowledge the synthesis of the 8-bromoflavone substrate is published only in Caddick's paper.[16]

First, their own initial investigations toward the synthesis of haloflavones have been conducted by using protocols based upon the classical Baker–Venkataraman O-acylation approach.[18] However, these reactions proved to be relatively low-yielding and slow to perform. At the end, the synthesis of 8-bromoflavone (**6**) was performed by the application of a C-acylation method described by Cushman[19] for the synthesis of hydroxylated flavones. The method required the utilization of lithium bis(trimethylsilyl)amide (LHMDS) at low temperature and 3′-bromo-2′-hydroxyacetophenone (**8**) as a starting material; however the source of compound **8** is not given in their article.

In this paper, we report on the synthesis of 8-bromoflavone (**6**) starting from the commercially available 2-bromophenol (**10**) and its Buchwald–Hartwig reaction with some aliphatic and aromatic amine derivatives.

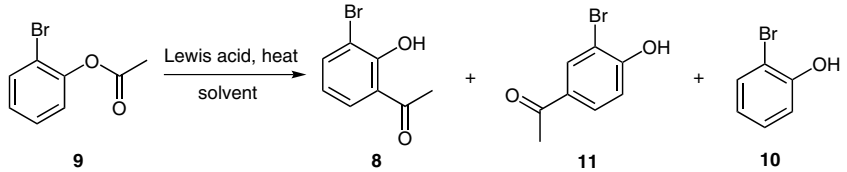
According to our retrosynthetic analysis, the synthesis of 8-bromoflavone (**6**) requires 3′-bromo-2′-hydroxyacetophenone (**8**) as a starting precursor, which can be prepared by Fries rearrangement of ester **9** after the acylation of the commercially available 2-bromophenol (**10**) (Scheme 2). The Claisen–Schmidt condensation of **8** with benzaldehyde results in the 2′-hydroxychalcone **7** and its oxidative ring closure could provide 8-bromoflavone (**6**).



Scheme 2 Retrosynthesis of 8-bromoflavone (**6**)

The esterification of 2-bromophenol (**10**) with acetyl chloride in the presence of triethylamine provided 2-bromophenyl acetate (**9**) in excellent yield (98%). After the first Fries rearrangement experiment of ester **9**, which was carried out under the usual neat conditions, revealed that optimization is required because the reaction resulted exclusively in 3′-bromo-4′-hydroxyacetophenone (**11**) and only traces of the desired 3′-bromo-2′-hydroxyacetophenone (**8**) was formed (Scheme 3).

In the case of nitrobenzene, 1,4-dioxane, and carbon disulfide, the formation of the desired compound **8** was not detected. The application of $ZnCl_2$ in nitrobenzene did not show even the formation of the *para*-substituted acetophenone **11**. Using different halogenated solvents acetophenone **8** was isolated in moderate yield. The rearrangement in *para*-position was successfully reduced providing acetophenone **8** by using aluminum trichloride in 1,2-dichlorobenzene at 140 °C (Table 1). Under these conditions, besides the by-product **11**, 2-bromophenol (**10**) was also detected in the reaction mixture, which could not be separated by using classical chromatographic solvents. The



Scheme 3 Fries rearrangement of ester **9**

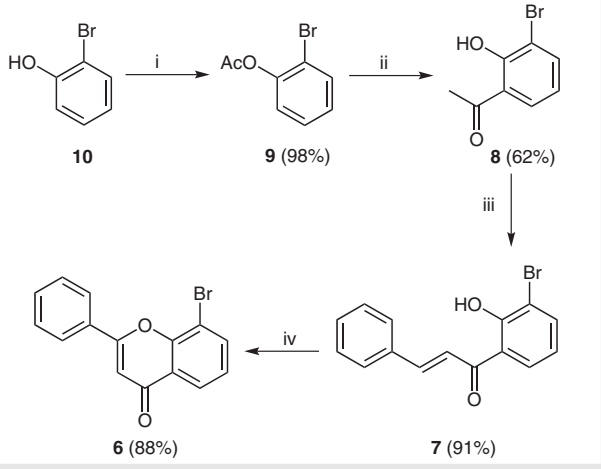
addition of triethylamine, as a basic component, to the dichloromethane (dichloromethane–triethylamine, 20:1) dramatically and solely reduced the retention factor of 2-bromophenol (**10**) (R_f = 0.65 → 0.15), therefore its separation from compound **8** became possible (see Figure 1 in Supporting Information).

Table 1 Optimization of the Synthesis of Acetophenone **8**

Solvent	Lewis acid	Temp (°C)	Time	Yield of **8** (%)[a]	**11**[b]	**10**[b]
neat	$AlCl_3$	100	3 h	trace	+	–
nitrobenzene	$ZnCl_2$	100	3 h	0	–	–
nitrobenzene	$AlCl_3$	100	45 min	0	+	–
1,4-dioxane	$AlCl_3$	100	3 h	0	–	–
carbon disulfide	$AlCl_3$	46	5 h	0	–	–
1,2-dichloroethane	$AlCl_3$	84	48 h	23	+	+
1,2-dichloroethane	$AlCl_3$	84	96 h	29	+	+
chlorobenzene	$AlCl_3$	130	3 h	37[c]	+	+
1,2-dichlorobenzene	$AlCl_3$	140	3 h	62	+	+

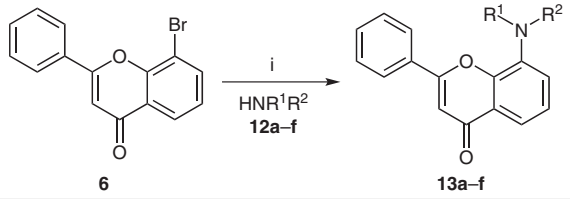
[a] Yields refer to pure isolated products.
[b] Identification by standard TLC monitoring; negative sign (–) : not isolated products.
[c] Large amount of *p*-acetylchlorobenzene was formed.

In the case of product **8**, the retention factor was changed to the higher position, that is, this compound does not behave as a phenolic compound, which phenomenon can be explained by the decreased acidity of the hydroxyl group due to the intramolecular chelate effect of the carbonyl group in compound **8**. The successfully separated 3′-bromo-2′-hydroxyacetophenone (**8**) was transformed into bromochalcone **7** with benzaldehyde by Claisen–Schmidt condensation. Using catalytic amount of iodine in hot dimethyl sulfoxide[20] the ring-closure of the chalcone derivative **7** provided the desired 8-bromoflavone (**6**) in high yield (Scheme 4).



Scheme 4 Synthesis of **6**. *Reagents and conditions*: (i) **10** (1.0 equiv), AcCl (1.1 equiv), Et_3N (1.1 equiv), r.t., CH_2Cl_2, 1 h; (ii) **9** (1.0 equiv), $AlCl_3$ (1.5 equiv), 1,2-dichlorobenzene, 140 °C, 3 h; (iii) **8** (1.0 equiv), PhCHO (1.5 equiv), KOH in 60% aq solution, EtOH, r.t., 24 h; (iv) **7** (1.0 equiv), I_2 (0.08 equiv), DMSO, 180 °C, 15 min.

The Buchwald–Hartwig reaction of **6** with amines **12a–f** (1.2 equiv) resulted in the aminated flavone derivatives **13a–f** in moderate and good yields (Scheme 5,Table 2). The reactions were carried out using $Pd_2(dba)_3$ (5 mol%) as the catalyst, BINAP (7.5 mol%) as the phosphane, and NaO*t*-Bu (1.4 equiv) as the base in anhydrous toluene at 110 °C.



Scheme 5 Synthesis of **13a–f**. *Reagents and conditions*: (i) **6** (1.0 equiv), $Pd_2(dba)_3$ (5 mol%), BINAP (7.5 mol%), amine **12a–f** (1.2 equiv), NaO*t*-Bu (1.4 equiv), anhydrous toluene, 110 °C, 3 h.

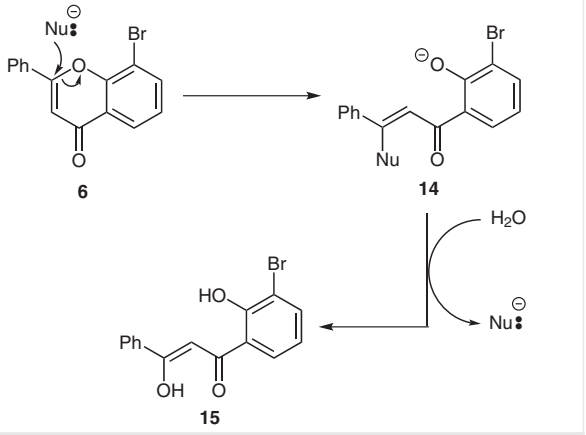
Table 2 Prepared Aminoflavones **13a–f**

12,**13**	R^1	R^2	Yield of **13** (%)[a]
a	Bu	H	51
b	Bn	H	66
c	4-ClC_6H_4	H	59
d	4-$MeOC_6H_4$	H	65
e	-$(CH_2)_2NMe(CH_2)_2$-		50
f	-$(CH_2)_2O(CH_2)_2$-		47

[a] Yields refer to pure isolated products.

Besides the desired product **13a–f**, 3′-bromo-2′-hydroxydibenzoylmethane (**15**) (and its tautomeric form) was observed. The appearance of this by-product can be explained by a concurrent ring-opening of the heterocycle under the applied basic conditions. As we have shown earlier,[17] a nucleophilic species, for example, *tert*-butoxide anion attacks the electrophilic carbon at positon 2 of the flavone moiety and the intermediate enol ether **14** hydrolyses during the workup and column chromatography on silica gel as shown in Scheme 6. After the isolation of **15**, its structure was elucidated by NMR, IR, and MS measurements.

All products were characterized by spectroscopic methods (NMR, IR, MS). The GC-MS measurements showed high purity, which was also proven by the sharp melting points. The yields indicated in Table 2 refer to pure isolated yields in all cases.



Scheme 6 Ring opening reaction of **6**

In conclusion, we have demonstrated the synthesis of 8-bromoflavone (**6**) from the commercially available 2-bromophenol through 3′-bromo-2′-hydroxyacetophenone (**8**), as a starting precursor. The synthesis of **8** was optimized and its further transformation to 8-bromoflavone (**6**) requires simple and convenient reaction conditions. Because the starting materials are easily accessible and the reactions give good yields, this new approach has potential applications in the synthesis of various functionalized flavones, which are of considerable interest as potential biologically active compounds or pharmaceuticals. The Buchwald–Hartwig amination of the prepared 8-bromoflavone (**6**) was studied with different primary and secondary amines. Further studies of the Buchwald–Hartwig reaction with different amino acid derivatives are currently underway in our laboratory.

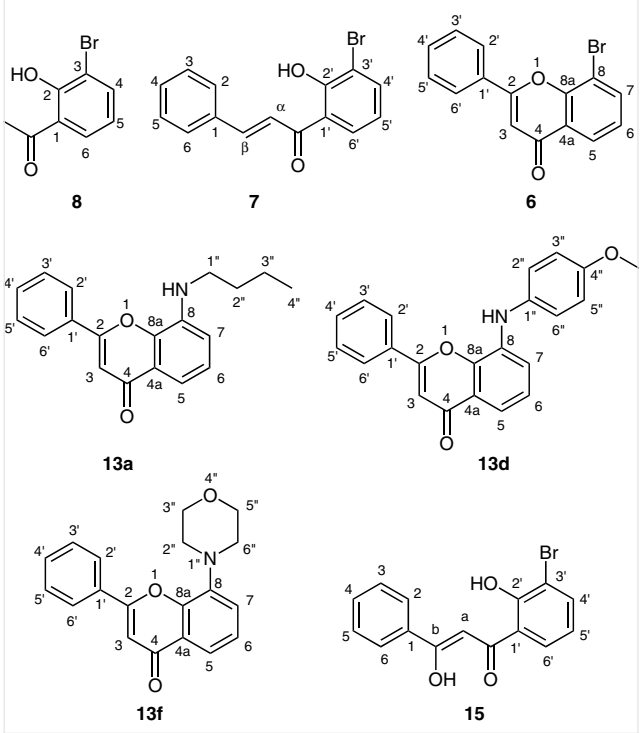


Figure 1 Atom-numbering for NMR assignments

Column chromatography was performed on silica gel (Merck 60, 70–230 mesh), eluents are given at the product description. TLC was performed on aluminum-backed TLC plates of silica gel 60 F254 (Merck, 0.2 mm) with the indicated eluent. The purity of the compounds was established by GC-MS (Agilent 7890, Agilent 5975 MS detector) with positive EI at 70 eV. NMR spectra were recorded on a Bruker AM 360 (360.13 MHz for ^{1}H, 90.03 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are given from internal $CHCl_3$ signals (δ = 7.26) for ^{1}H NMR and (δ = 77.00) for ^{13}C NMR. Coupling constants (*J* in Hz) are accurate to ± 0.2 Hz for ^{1}H NMR data. Atom-numbering is given in Figure 1. Melting points were determined using Büchi B-540 equipment. Elemental analyses (C, H) were conducted using the Elementar Vario MicroCube instrument. IR spectra were recorded as KBr disc on a PerkinElmer FT-IR 16PC or Jasco FT-IR 4100A equipment.

3′-Bromo-2′-hydroxyacetophenone (8)

To a solution of commercially available 2-bromophenol (**10**; 10.0 g, 57.8 mmol) in anhydrous CH_2Cl_2 (50 mL) in a round-bottom flask were added AcCl (5.0 g, 63.6 mmol) and Et_3N (4.67 mL, 63.6 mmol) and the mixture was stirred at r.t. for 1 h. The solvent was evaporated under reduced pressure to give the pure 2′-bromophenylacetate (**9**; 12.18 g, 56.6 mmol, 98%). The ester **9** was dissolved in 1,2-dichlorobenzene (100 mL), then $AlCl_3$ (11.3 g, 84.9 mmol) was added. The mixture was heated and stirred at 140 °C for 3 h. Ice and 10% HCl were added till the solution was slightly acidic (pH). 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 CH_2Cl_2 was evaporated under vacuum. The crude residue was treated with hexane (300 mL) and cooled at –20 °C when most of the *para*-substituted by-product **11** crystallized and filtered off. The solution was filtered through silica gel and washed with hexane till the 1,2-dichlorobenzene was eluted, then the eluent was changed to CH_2Cl_2–Et_3N (20:1). After chromatography and evaporation of the eluent, the pure product **8** was isolated as a colorless oil; yield: 7.55 g (35.1 mmol, 62%).

IR (ATR): 3008, 2925, 2570, 1643, 1473, 1428, 1364, 1250, 1146, 1071, 968, 836, 775, 738, 627, 595, 523, 437 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 12.97 (s, 1 H, OH), 7.73 (m, 2 H, 4-H, 6-H), 6.82 (t, *J* = 7.9 Hz, 1 H, 5-H), 2.66 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 204.3 (C=O), 158.9 (C-2), 139.6 (C-4),129.9 (C-6), 120.5 (C-1), 119.6 (C-5), 112.0 (C-3), 26.7 (CH_3).

MS: *m*/*z* = 214 [M$^{+\cdot}$], 216 [M$^{+\cdot}$ + 2, 100%], 201, 199, 143, 145, 92, 77, 63.

Anal. Calcd for $C_8H_7BrO_2$: C, 44.68; H, 3.28. Found: C, 44.50; H, 3.19.

3′-Bromo-2′-hydroxychalcone (7)

To a solution of **8** (7.55 g, 35.1 mmol) in EtOH (40 mL) were added benzaldehyde (5.4 mL, 52.6 mmol) and 60% aq KOH (45 mL, 0.8 mol, 22 equiv). The orange solution was stirred for 30 min and allowed to stand overnight at r.t. 10% aq HCl was added until the solution

reached pH 1, the precipitate was collected by filtration, and washed with H_2O (250 mL) to give **7** as yellow crystals; yield: 9.68 g (31.9 mmol, 91%); mp 116–119 °C.

IR (ATR): 3443, 3063, 2858, 2768, 1948, 1639, 1573, 1472, 1425, 1333, 1226, 1145, 1044, 978, 858, 756, 700, 580 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 13.61 (s, 1 H, OH), 7.96 (d, *J* = 15.4 Hz, 1 H, β-H), 7.90 (dd, *J* = 8.0, 1.1 Hz, 1 H, 5-H), 7.76 (dd, *J* = 7.8, 0.9 Hz, 1 H, 7-H), 7.65 (m, 3 H, 2,6-H, α-H), 7.45 (m, 3 H, 3,5-H, 4-H), 6.86 (t, *J* = 7.9 Hz, 1 H, 6-H).

^{13}C NMR ($CDCl_3$): δ = 193.3 (C=O), 160.0 (C-2′), 146.6 (C-β),139.4 (C-4′), 134.3 (C-1), 131.3 (C-4), 129.1 (C-3,5),128.8 (C-2,6, C-6′), 120.8 (C-1′), 119.5 (C-α), 119.4 (C-5′), 112.3 (C-3′).

MS: *m*/*z* = 302 [$M^{+\cdot}$], 304 [$M^{+\cdot}$ + 2], 303 [M + H^+, 100%], 305 [M + $H^{+\cdot}$ + 2], 287, 285, 227, 225, 200, 198, 165, 145, 143, 131, 119, 103, 92, 77, 63, 51.

Anal. Calcd for $C_{15}H_{11}BrO_2$: C, 59.43; H, 3.66. Found: C, 59.31; H, 3.56.

8-Bromoflavone (6)

To a solution of **7** (9.68 g, 31.9 mmol) in DMSO (60 mL) was added I_2 (650 mg, 2.55 mmol) and the mixture was mildly refluxed for 15 min. The mixture was poured into 10% aq Na_2SO_3 (300 mL) and stirred. The solid product **6** was collected by filtration and recrystallized from hexane–acetone (5:1); yield: 8.46 g (28.1 mmol, 88%); white solid; mp 181.0–182.0 °C.

IR (ATR): 3444, 3070, 2309, 1959, 1646, 1472, 1370, 1236, 1103, 1068, 1021, 916, 853, 771, 689, 627, 518, 503, 451, 418 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.14 (m, 3 H, 5-H, 2′,6′-H), 8.01 (d, *J* = 7.9 Hz, 1 H, 7-H), 7.62 (m, 3 H, 3′,5′-H, 4′-H), 7.43 (t, *J* = 7.9 Hz, 1 H, 6-H), 7.15 (s, 1 H, 3-H).

^{13}C NMR ($CDCl_3$): δ = 176.6 (C-4), 162.4 (C-2), 152.0 (C-8a), 137.4 (C-7), 132.1 (C-4′), 130.7 (C-1′), 129.2 (C-3′,5′), 126.4 (C-5), 126.3 (C-2′,6′), 124.7 (C-4a), 124.5 (C-6), 111.5 (C-8), 106.9 (C-3).

MS: *m*/*z* = 300 [$M^{+\cdot}$], 302 [$M^{+\cdot}$ + 2, 100%], 274, 272, 200, 198, 172, 170, 137, 135, 119, 102, 82, 63.

Anal. Calcd for $C_{15}H_9BrO_2$: C, 59.83; H, 3.01. Found: C, 59.78; H, 2.98.

8-Alkyl-/Arylaminoflavones 13a–f; General Procedure

To a mixture of 8-bromoflavone (**6**; 200 mg, 0.66 mmol), NaO*t*-Bu (88 mg, 0.92 mmol), BINAP (32 mg, 0.050 mmol), and amine **12a**–**f** (0.80 mmol) in anhydrous toluene (6 mL) in a dried flask was added $Pd_2(dba)_3$ (30 mg, 0.032 mmol) under N_2. The reaction mixture was stirred and refluxed at 110 °C for 3 h in an oil bath. The crude reaction mixture was filtered on silica gel eluting with pure acetone. To the filtrate was added a small amount of silica gel and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give the pure cross-coupled product **13a**–**f** as yellow solids.

Only representative examples are given below, the vast majority of the characterizations are presented in the Supporting Information.

8-(Butylamino)flavone (13a)

Eluent: toluene–EtOAc (8:1); yield: 99 mg (51%); mp 91.5–93.5 °C.

IR (ATR): 3444, 3061, 2961, 2931, 2857, 1904, 1815, 1638, 1590, 1483, 1452, 1375, 1309, 1212, 1149, 1043, 878, 771, 738, 687, 536, 501 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.83 (m, 2 H, 2′,6′-H), 7.54 (m, 3 H, 3′,5′-H, 4′-H), 7.48 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.25 (t, *J* = 7.9 Hz, 1 H, 6-H), 6.89 (d, *J* = 7.9 Hz, 1 H, 7-H), 6.77 (s, 1 H, 3-H), 4.45 (s, 1 H, NH), 3.28 (m, 2 H, 1″H), 1.74 (pent, *J* = 7.2 Hz, 2 H, 2″-H), 1.51 (s, *J* = 7.2 Hz, 2 H, 3″-H), 1.02 (t, *J* = 7.2 Hz, 2 H, 4″-H).

^{13}C NMR ($CDCl_3$): δ = 178.8 (C-4), 162.4 (C-2), 144.8 (C-8a), 138.1 (C-8), 132.3 (C-1′), 131.4 (C-4′), 129.2 (C-3′,5′), 126.2 (C-2′,6′), 125.6 (C-6), 123.8 (C-4a), 112.9 (C-7), 111.7 (C-5), 108.0 (C-3), 43.5 (C-1″, 31.5 (C-2″), 20.4 (C-3″), 13.9 (C-4″).

MS: *m*/*z* = 293 [$M^{+\cdot}$], 250 (100%), 148, 107, 65.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.75; H, 6.50; N, 4.73.

8-[(4-Methoxyphenyl)amino]flavone (13d)

Eluent: toluene–EtOAc (8:1); yield: 148 mg (65%); mp 170.0–172.0 °C.

IR (ATR): 3424, 3298, 3004, 2951, 2830, 2320, 2062, 1633, 1582, 1509, 1379, 1244, 1042, 896, 826, 770, 687, 546, 508, 453 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.85 (m, 2 H, 2′,6′-H), 7.60 (dd, *J* = 7.4, 1.8 Hz, 1 H, 5-H), 7.52 (m, 3 H, 3′,5′-H, 4′-H), 7.21 (m, 4 H, 6-H, 7-H, 2″,6″-H), 6.94 (d, *J* = 8.8 Hz, 2 H, 3″,5″-H), 6.79 (s, 1 H, 3-H), 6.16 (s, 1 H, NH), 3.83 (s, 3 H, OCH_3).

^{13}C NMR ($CDCl_3$): δ = 178.6 (C-4), 162.6 (C-2), 156.7 (C-4″), 145.5 (C-8a), 135.9 (C-1″), 133.8 (C-8), 132.1 (C-1′), 131.5 (C-4′), 129.1 (C-3′,5′), 126.3 (C-2′,6′), 125.2 (C-6), 124.6 (C-2′,6′), 124.4 (C-4a), 116.1 (C-7), 115.0 (C-3″,5″), 114.4 (C-5), 108.0 (C-3), 55.6 (OCH_3).

MS: *m*/*z* = 343 [$M^{+\cdot}$, 100%], 328, 226, 170, 142, 120, 77.

Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.85; H, 4.94; N, 4.03.

8-Morpholinoflavone (13f)

Eluent: toluene–EtOAc (4:1); yield: 96 mg (47%); mp 200.0–202.0 °C.

IR (ATR): 3433, 3059, 2972, 2846, 2830, 2753, 1638, 1576, 1485, 1447, 1376, 1240, 1113, 983, 855, 775, 749, 689, 629, 532, 501, 458, 438 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.06 (m, 2 H, 2′,6′-H), 7.65 (m, 4 H, 5-H, 3′,5′-H, 4′-H), 7.41 (m, 2 H, 6-H, 7-H), 7.09 (s, 1 H, 3-H), 3.90 (m, 2 H, 3″,5″-H), 3.17 (m, 2 H, 2″,6″-H).

^{13}C NMR (DMSO-d_6): δ = 177.5 (C-4), 161.9 (C-2), 149.0 (C-8a), 141.9 (C-8), 131.8 (C-4′), 131.4 (C-1′), 129.3 (C-3′,5′), 126.1 (C-2′,6′), 125.4 (C-6), 124.3 (C-4a), 122.5 (C-7), 117.7 (C-5), 106.7 (C-3), 66.4 (C-3″,5″), 51.4 (C-2″,6″).

MS: *m*/*z* = 307 [$M^{+\cdot}$, 100%], 276, 249, 231, 165, 147, 119, 92.

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.18; H, 5.50; N, 4.50.

(3-Bromo-2-hydroxyphenyl)-3-hydroxy-3-phenylprop-2-en-1-one (15)

This compound was obtained as a by-product from the reaction of amines and 8-bromoflavone (**6**) in a varying yield of 10–30%; eluent: toluene–EtOAc (8:1); yellow crystals; mp 136.0–138.5 °C.

IR (ATR): 3442, 3057, 2923, 2852, 1609, 1576, 1479, 1320, 1240, 1178, 1099, 1057, 884, 756, 706, 681, 623 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 15.34 (s, 1 H, β-OH), 12.87 (1 H, s, 2′-OH), 7.94 (d, *J* = 7.6 Hz, 2 H, 2,6-H), 7.74 (m, 3 H, 3,5-H, 4-H), 7.50 (m, 2 H, 4′-H, 6′-H), 6.83 (m, 2 H, 5′-H, α-H).

^{13}C NMR ($CDCl_3$): δ = 194.8 (C=O), 180.0 (C-β), 158.9 (C-2′), 138.9 (C-4′), 133.3 (C-1), 132.7 (C-4), 128.8 (C-3,5), 127.7 (C-6′), 126.9 (C-2,6), 120.0 (C-1′), 119.7 (C-5′), 112.5 (C-3′), 92.3 (C-α).

MS: *m*/*z* = 318 [$M^{+\cdot}$], 320 [$M^{+\cdot}$ + 2], 121, 199, 105 (100%), 77, 51.

Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47. Found: C, 56.38; H, 3.40.

Acknowledgment

Financial support from the Hungarian Scientific Research Fund (OTKA) (grant number K75806 and grant number PD 106244) is greatly appreciated.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560325.

References

(1) (a) Harborne, J. B.; Baxter, H. *The Handbook of Natural Flavonoids*; Vol. 1; Wiley: Chichester, **1999**. (b) *Römpp Lexikon Naturstoffe*; Steglich, W.; Fugmann, B.; Lang-Fugmann, S., Eds.; Thieme: Stuttgart, **1997**. (c) Middleton, E. Jr.; Kandaswami, C.; Theoharides, T. C. *Pharmacol. Rev.* **2000**, *52*, 672. (d) Beecker, G. R. *J. Nutr.* **2003**, *133*, 3248S. (e) Harborne, J. B.; Williams, C. A. *Phytochemistry* **2000**, *55*, 481. (f) Havsteen, B. H. *Pharmacol. Ther.* **2002**, *96*, 67.

(2) (a) Rao, Y. K.; Fang, S. H.; Tzeng, Y. M. *Bioorg. Med. Chem.* **2005**, *13*, 6850. (b) Gao, G. Y.; Li, D. J.; Keung, W. M. *J. Med. Chem.* **2001**, *44*, 3320. (c) Su, B.; Hackett, J. C.; Diaz-Cruz, E. S.; Kim, Y. W.; Brueggemeier, R. W. *Bioorg. Med. Chem.* **2005**, *13*, 6571. (d) Gao, H.; Kawabata, J. *Bioorg. Med. Chem.* **2005**, *13*, 1661. (e) Wang, S. F.; Jiang, Q.; Ye, Y. H.; Li, Y.; Tan, R. X. *Bioorg. Med. Chem.* **2005**, *13*, 4880. (f) Kim, Y. W.; Hackett, J. C.; Brueggemeier, R. W. *J. Med. Chem.* **2004**, *47*, 4032. (g) Traxler, P.; Green, J.; Mett, H.; Sequin, U.; Furet, P. *J. Med. Chem.* **1999**, *42*, 1018. (h) Daskiewies, J.; Depeint, F.; Viornery, L.; Bayet, C.; Geraldine, C.; Comte, G.; Gee, J.; Johnson, I.; Ndjoko, K.; Hostettmann, K.; Barron, D. *J. Med. Chem.* **2005**, *48*, 2790.

(3) (a) Cushman, M.; Nagarathnam, D.; Burg, D. L.; Geahlen, R. L. *J. Med. Chem.* **1991**, *34*, 798. (b) Cushman, M.; Zhu, H.; Geahlen, R. L.; Kraker, A. J. *J. Med. Chem.* **1994**, *37*, 3353.

(4) Ahn, Y. M.; Vogeti, L.; Liu, C-J.; Santhapuram, H. K. R.; White, J. M.; Vasandani, V.; Mitscher, L. A.; Lushington, G. H.; Hanson, P. R.; Powell, D. R.; Himes, R. H.; Roby, K. F.; Ye, Q.; Georg, G. I. *Bioorg. Med. Chem.* **2007**, *15*, 702.

(5) (a) Akama, T.; Ishida, H.; Shida, Y.; Kimura, U.; Gomi, K.; Saito, H.; Fuse, E.; Kobayashi, S.; Yoda, N.; Kasai, M. *J. Med. Chem.* **1997**, *40*, 1894. (b) Shida, Y.; Sugaya, T.; Gomi, K.; Kasai, M.; Morimoto, M. Patent EP 374789, **1990**; *Chem. Abstr.* **1990**, 631085. (c) Akama, T.; Shida, Y.; Sugaya, T.; Ishida, H.; Gomi, K.; Kasai, M. *J. Med. Chem.* **1996**, *39*, 3461.

(6) Vasselin, D. A.; Westwell, A. D.; Matthews, C. S. *J. Med. Chem.* **2006**, *49*, 3973.

(7) Dauzonne, D.; Folléas, B.; Martinez, L.; Chabot, G. G. *Eur. J. Med. Chem.* **1997**, *32*, 71.

(8) Larget, R.; Lockhart, B.; Renard, P.; Largeron, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 835.

(9) (a) Baker, W. *J. Chem. Soc.* **1933**, 1381. (b) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767.

(10) (a) Wurm, G.; Geres, U. *Arch. Pharm. (Weinheim)* **1978**, *311*, 177. (b) Cardenas, M.; Marder, M.; Blank, V. C.; Roguin, L. P. *Bioorg. Med. Chem.* **2006**, *14*, 2966. (c) Wurm, G.; Geres, U. *Arch. Pharm. (Weinheim)* **1977**, *310*, 609. (d) Tang, L.; Zhang, S.; Yang, J.; Gao, W.; Cui, J.; Zhuang, T. *Molecules* **2004**, *9*, 842. (e) Görlitzer, K. *Arch. Pharm. (Weinheim)* **1979**, *312*, 248. (f) Wurm, G.; Geres, U. *Arch. Pharm. (Weinheim)* **1976**, *309*, 273.

(11) (a) Schmidt, J. G. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1459. (b) Claisen, L.; Claparède, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2460.

(12) (a) Reichel, L.; Hampel, G. *Liebigs Ann. Chem.* **1966**, *693*, 216. (b) Raval, A. A.; Shah, N. M. *J. Org. Chem.* **1956**, *21*, 1408. (c) Agrawal, N. N.; Soni, P. A. *Indian J. Chem.* **2005**, *44B*, 2601. (d) Eiden, F.; Patzelt, G.; Buchborn, H. *Arch. Pharm. (Weinheim)* **1989**, *322*, 589. (e) Lorenz, M.; Kabir, M. S.; Cook, J. M. *Tetrahedron Lett.* **2010**, *51*, 1095. (f) Cheng, Y.-M.; Pu, S.-C.; Yu, Y.-C.; Chou, P.-T.; Huang, C.-H.; Chen, C.-T.; Li, T.-H.; Hu, W.-P. *J. Phys. Chem. A* **2005**, *109*, 11696. (g) Rastogi, M. K.; Chaudhary, K.; Kapoor, R. P.; Garg, C. P. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1978**, *16*, 895.

(13) Quintin, J.; Ruillier, C.; Thoret, S.; Lewin, G. *Tetrahedron* **2006**, *62*, 4038.

(14) (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (e) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (f) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (g) Hartwig, J. F. *Synlett* **1997**, 329. (h) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (i) Guram, S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (j) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (k) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, **2004**, Chap. 13, 699–760.

(15) Deng, B.-L.; Lepoivre, J. A.; Lemiere, G. *Eur. J. Org. Chem.* **1999**, 2683.

(16) Fitzmaurice, R. J.; Etheridge, Z. C.; Jumel, E.; Woolfson, D. N.; Caddick, S. *Chem. Commun.* **2006**, 4814.

(17) Kónya, K.; Pajtás, D.; Kiss-Szikszai, A.; Patonay, T. *Eur. J. Org. Chem.* **2015**, 828.

(18) Ares, J. J.; Outt, P. E.; Kakodkar, S. V.; Buss, R. C.; Geiger, J. C. *J. Org. Chem.* **1993**, *58*, 7903.

(19) Cushman, M.; Nagarathnam, D. *Tetrahedron Lett.* **1990**, *31*, 6497.

(20) (a) Fekete, Sz.; Patonay, T.; Silva, A. M. S.; Cavaleiro, J. A. S. *ARKIVOC* **2012**, *(v)*, 210. (b) Dao, T. T.; Chi, Y. S.; Kim, J.; Kim, H. P.; Kim, S.; Park, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1165. (c) Cabrera, M.; Simoens, M.; Falchi, G.; Lavaggi, M. L.; Piro, O. E.; Castellano, E. E.; Vidal, A.; Azqueta, A.; Monge, A.; Ceráin, A. L.; Sagrera, G.; Seoane, G.; Cerecettoa, H.; González, M. *Bioorg. Med. Chem.* **2007**, *15*, 3356. (d) Chimenti, F.; Fioravanti, R.; Bolasco, A.; Chimenti, P.; Secci, D.; Rossi, F.; Yáñez, M.; Orallo, F.; Ortuso, F.; Alcaro, S.; Cirilli, R.; Ferretti, R.; Sanna, M. L. *Bioorg. Med. Chem.* **2010**, *18*, 1273.