A Scaffold Approach to 3,6,8-Trisubstituted Flavones

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Abstract: An efficient synthetic approach to 3,6,8-trisubstituted flavone scaffolds has been developed based on Pd-mediated coupling reactions.

Key words: catalysis, flavone, Heck reaction, palladium, scaffold, Stille reaction

Flavone derivatives (Figure 1) are widely distributed in nature and have an interesting range of biological activities,[1] including anti-cancer,[2–4] anti-HIV,[5] and anti-oxidant[6] properties. In addition, the powerful fluorescent properties of 3-hydroxyflavones have recently been demonstrated.[7] Flavones and chromones have also been considered as privileged structures in drug discovery.[8] We have for some time been interested in the synthesis of functionalized chromones and flavones and their use in different pharmacological/biological applications. In the present study we have focussed our attention on the synthesis of 3,6,8-substituted flavones. We have developed a scaffold approach to produce a diverse series of such derivatives. Careful choice of reaction conditions in palladium-mediated reactions allows the regioselective introduction of alkyl substituents with or without heterofunctionalities.

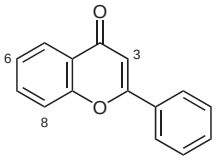
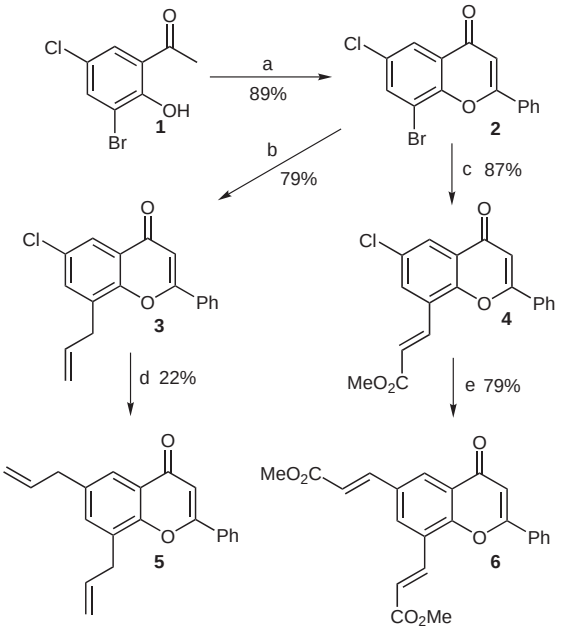


Figure 1 Structure and numbering of the flavone system

Our synthetic strategy was based on the use of compound **1** as starting material (Scheme 1). From **1** it is possible to synthesize both flavone **2** (Scheme 1) and flavonol **8** (Scheme 3). These derivatives contain functionalities that allow further chemical transformations by selective palladium-mediated coupling reactions. Our first aim was to find the optimal reaction conditions for regioselective introduction of substituents in the 6- and 8-positions of 8-bromo-6-chloroflavone (**2**). Compound **2**[9] was prepared from **1** via esterification of the phenol with benzoyl chloride followed by a Baker–Venkataraman rearrangement in excellent yield (93% over two steps).[10] The cyclization was performed using HCl in refluxing AcOH (82%). The difference in reactivity between aryl chlorides and bromides in palladium-catalyzed reactions should make it possible to obtain complete selectivity in reactions in the 6- and 8-positions.[11] Two different types of palladium reactions were tested, the Stille cross-coupling[12] and the Heck reaction.[13] The Heck reaction was run using methyl acrylate, $Pd(OAc)_2$ and tri(*o*-tolyl)phosphine in DMF with Et_3N as the base under microwave heating to provide **4** in good yield (87%).[14] According to ^1H NMR spectral analysis of the crude reaction mixture the product was formed in an *E*/*Z* isomeric ratio of 95:5. The corresponding Stille coupling using allyltributyltin as reagent and $Pd(PPh_3)_4$ as catalyst in dioxane afforded **3** in 79% yield without any sign of reaction in the 6-position.[15] Thus, Pd-catalyzed reactions in the 8-position of **2** were possible, in good yields and with exellent regioselectivity.

Previous studies have shown that it is possible to obtain efficient palladium-catalyzed coupling reactions of aryl chlorides using the electron-rich and sterically hindered P(*t*-Bu)$_3$ as a ligand.[16] In the same study it was also shown



Scheme 1 *Reagents and conditions*: (a) i. benzoyl chloride, pyridine, r.t., 1 h; ii. KOH, pyridine, 50 °C, 2 h; (iii) HCl, AcOH, reflux, 14 h; (b) allylSnBu$_3$, $Pd(PPh_3)_4$, dioxane, 80 °C, 14 h; (c) methyl acrylate, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, DMF, 160 °C, 30 min, microwave; (d) allylSnBu$_3$, $Pd_2(dba)_3$, P(*t*-Bu)$_3$, dioxane, 80 °C, 14 h; (e) methyl acrylate, $Pd_2(dba)_3$, [P(*t*-Bu)$_3$H]BF$_4$, Et_3N, dioxane, 160 °C, 30 min, microwave.

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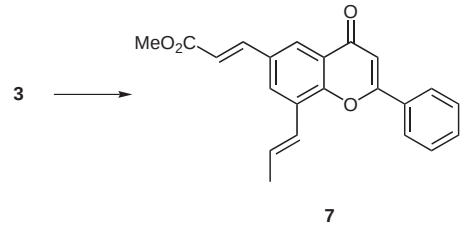
that CsF as additive facilitates the coupling. However, reacting **3** with allylSnBu$_3$, Pd$_2$(dba)$_3$, P(*t*-Bu)$_3$ and CsF in dioxane at 80 °C for 14 hours did not afford any of the desired product. Using the same reaction conditions but without CsF gave **5** in 22% yield.[17,18]

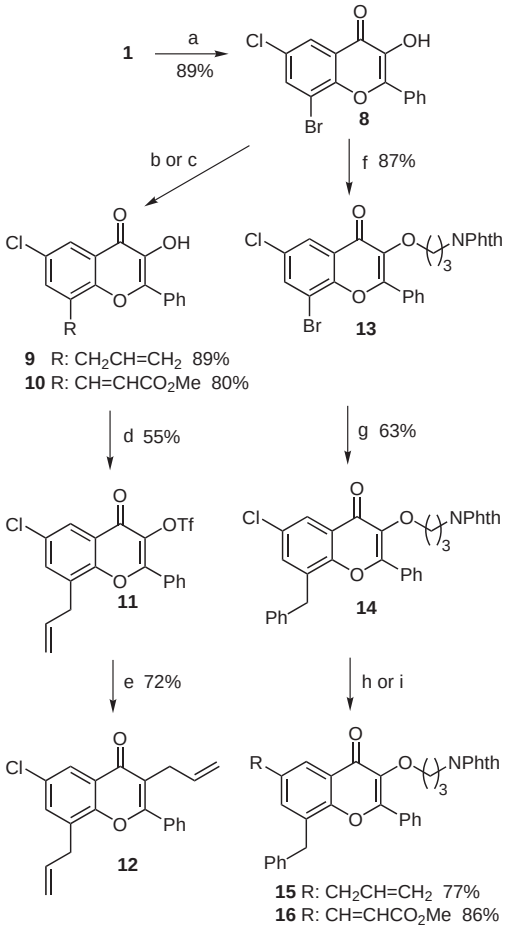
A Heck reaction of aryl chloride **4** together with Pd$_2$(dba)$_3$, [P(*t*-Bu)$_3$H]BF$_4$ and Et$_3$N using microwave heating gave **6** in good yield (79%).[19] However, applying the same reaction conditions to **3** gave **7** in 57% yield (Scheme 2). Compound **7** resulted from a Heck reaction together with a Pd-mediated rearrangement of the double bond in the allyl group. In these Heck reactions the phosphine ligand was added as the [P(*t*-Bu)$_3$H]BF$_4$ salt which is more stable and easier to handle than the phosphine itself. Previous studies have shown that Cs$_2$CO$_3$ should be the base of choice for Heck reactions on aryl chlorides.[20] Unfortunately, using Cs$_2$CO$_3$ in reactions of **4** to **6** did not result in any product formation.



Scheme 2 *Reagents and conditions*: methyl acrylate, Pd$_2$(dba)$_3$, [P(*t*-Bu)$_3$H]BF$_4$, dioxane, 160 °C, 30 min, microwave (57%).

Our second aim was to develop a convenient method to introduce different substituents in the 3-position of the flavone system (Scheme 3). This has been achieved either via O-alkylation reactions using different alkyl halides in the presence of base[5,21] or via palladium-catalyzed Sonogashira and Suzuki reactions on the corresponding iodide[22] or bromide.[23] We planned to use the corresponding triflate in Stille reactions. Triflates have been successfully used in palladium-mediated coupling reactions in other aromatic systems.[24,25] First, 8-bromo-6-chloro-3-hydroxyflavone (**8**) was prepared from **1** with benzaldehyde and KOH in ethanol to give an intermediate chalcone which was cyclized using NaOH/H$_2$O$_2$ to afford **8** in excellent yield (89% over two steps).[5,26] The triflate of **8** was synthesized using triflic anhydride and pyridine in dichloromethane (67%). Previous studies have shown that it is possible to obtain selectivity between triflates and bromides in palladium-catalyzed coupling reactions.[24] However, when using the triflate in a Stille coupling we observed that the regioselectivity was low as mixtures of products originating from reactions in either the 3- or the 8-positions (or both) were isolated. Thus, the reactivity of triflate and bromide seems to be similar in the flavone system. As the reactivity difference is expected to be larger between triflate and chloride it would be an advantage to carry out the coupling reaction in position 8 prior to conversion of the hydroxy group into a triflate. A Stille coupling using allyltributyltin as reagent and Pd(PPh$_3$)$_4$ as catalyst in dioxane at 80 °C gave **9** in good yield (89%). A Heck reaction using methyl acrylate, Pd(OAc)$_2$, tri(*o*-tolyl)phosphine and Et$_3$N as a base in DMF gave **10** (80%). Compound **9** was then converted to the triflate **11** (55%) which was used in a Stille coupling with allyltributyltin and Pd(PPh$_3$)$_4$ in dioxane to afford **12** (72%) without any sign of rearrangement of the allyl group in the 8-position.

Modification of the 3-hydroxy group by alkylation was also accomplished by reacting **8** with *N*-(3-bromopropyl)phthalimide and K$_2$CO$_3$ in DMF to obtain **13** in 87% yield.[27] Thereafter, a benzyl group was introduced in the 8-position by a Stille coupling using benzyltributyltin as reagent and Pd(PPh$_3$)$_4$ as catalyst in DMF at 60 °C to afford **14** (63%). A second coupling reaction was then performed in the 6-position; a Stille coupling was run with



Scheme 3 *Reagents and conditions*: (a) i. benzaldehyde, KOH, EtOH, 50 °C for 3 h, then r.t. for 14 h; ii. NaOH, H$_2$O$_2$, THF–MeOH–H$_2$O, 0 °C then r.t. for 14 h; (b) allylSnBu$_3$, Pd(PPh$_3$)$_4$, dioxane, 80 °C, 14 h; (c) methyl acrylate, Pd(OAc)$_2$, P(*o*-tolyl)$_3$, Et$_3$N, DMF, 160 °C, 30 min, microwave; (d) Tf$_2$O, pyridine, CH$_2$Cl$_2$, 0 °C then r.t. for 14 h; (e) allylSnBu$_3$, Pd(PPh$_3$)$_4$, dioxane, 150 °C, 30 min, microwave; (f) *N*-(3-bromopropyl)phthalimide, K$_2$CO$_3$, DMF, 50 °C, 15 h; (g) benzylSnBu$_3$, Pd(PPh$_3$)$_4$, DMF, 60 °C, 14 h; (h) allylSnBu$_3$, Pd$_2$(dba)$_3$, P(*t*-Bu)$_3$, dioxane, 80 °C, 14 h; (i) methyl acrylate, Pd$_2$(dba)$_3$, [P(*t*-Bu)$_3$H]BF$_4$, Et$_3$N, dioxane, 160 °C, 30 min, microwave; (Phth = phthalimide).

allyltributyltin, $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ in dioxane to produce **15** (77%) and a Heck reaction using $Pd_2(dba)_3$, $[P(t\text{-}Bu)_3H]BF_4$, Et_3N and methyl acrylate in dioxane to obtain **16** (86%).

Deprotection of the phthalimide to obtain the corresponding amine is possible using ethylene diamine in refluxing ethanol. As an example **14** was deprotected using this procedure, the primary amine was not isolated but directly protected with a Boc group in good yield (87% over two steps).

In conclusion, we have developed an efficient strategy to obtain 3,6,8-trisubstituted flavone derivatives using Pd-mediated coupling reactions. We have used a scaffold that makes it possible to selectively introduce different substituents in the 3-, 6- and 8-positions. This strategy is expected to be general also for other flavone derivatives with different substitution patterns and should be possible to use for the production of series of structurally diverse derivatives of interest in many different pharmacological and biological applications. Synthesis of such derivatives is presently under way in our laboratory.

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(14) **General Procedure for the Heck Reaction in Position 8 – Synthesis of 6-Chloro-8-(2-methoxycarbonylethenyl)-flavone (4).**
A solution of **2** (150 mg, 0.45 mmol), $Pd(OAc)_2$ (10 mg, 0.045 mmol), Pd(*o*-tolyl)$_3$ (30 mg, 0.9 mmol), Et_3N (0.12 mL, 0.9 mmol) and methyl acrylate (0.08 mL, 0.9 mmol) in DMF (4 mL) in a microwave tube was heated in a microwave cavity for 30 min at 160 °C. The solution was filtered through Celite® and H_2O (10 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were dried over anhyd Na_2SO_4 before the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to afford 133 mg (87%) of **4** as a light-yellow powder; mp 181–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 6.66 (d, *J* = 16.1 Hz, 1 H), 6.84 (s, 1 H), 7.56–7.59 (m, 3 H), 7.86 (d, *J* = 2.6 Hz, 1 H), 7.90–7.92 (m, 2 H), 8.21 (d, *J* = 2.6 Hz, 1 H), 8.21 (d, *J* = 16.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.3, 108.0, 122.7, 125.7, 126.6, 126.8, 127.1, 129.6, 131.4, 131.5, 131.8, 132.3, 135.7, 152.5, 163.9, 166.7, 176.9. Anal. Calcd for $C_{19}H_{13}ClO_4$: C, 66.97, H, 3.85. Found: C, 66.82, H, 3.77.
(15) **General Procedure for Stille Coupling in Positions 3 and 8 – Synthesis of 8-Allyl-6-chloro-flavone (3).**
A solution of **2** (400 mg, 1.2 mmol), $Pd(PPh_3)_4$ (140 mg, 0.12 mmol) and allyltributyltin (600 mg, 1.8 mmol) in dioxane (30 mL) under N_2 was warmed to 80 °C for 14 h. The mixture was allowed to cool to r.t. and filtered through Celite®. A sat. aq KF solution (15 mL) was added and stirred for 30 min. The solution was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phases were washed with H_2O (2 × 10 mL), dried over anhyd $MgSO_4$ before the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to afford 282 mg (79%) of **3** as a white powder; mp 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (d, *J* = 6.6 Hz, 2 H), 5.19–5.25 (m, 2 H), 6.01–6.12 (m, 1 H), 6.83 (s, 1 H), 7.50 (d, *J* = 2.6 Hz, 1 H), 7.54–7.57 (m, 3 H), 7.89–7.91 (m, 2 H), 8.07 (d, *J* = 2.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.9, 107.5, 118.1, 123.4, 125.1, 126.4, 129.4, 131.1, 131.8, 132.0, 134.2, 134.5, 152.8, 163.4, 177.6. Anal. Calcd for $C_{18}H_{13}ClO_2$: C, 72.85, H, 4.42. Found: C, 72.67, H, 4.35.
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(17) **General Procedure for the Stille Coupling in Position 6 – Synthesis of 6,8-Diallyl-flavone (5).**
A solution of **3** (51 mg, 0.17 mmol), allyltributyltin (85 mg, 0.26 mmol), $Pd_2(dba)_3$ (10 mg, 0.01 mmol) and P(*t*-Bu)$_3$ (8 mg, 0.04 mmol) in dioxane (15 mL) under N_2 was warmed to 80 °C for 14 h. The mixture was allowed to cool to r.t. and

filtered through Celite®. A sat. aq KF solution (10 mL) was added and stirred for 30 min. The solution was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were washed with H_2O (2 × 10 mL), dried over anhyd $MgSO_4$ before the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel using a manual gradient of CH_2Cl_2–Et_2O (100:0 to 95:5) as eluent to afford 12 mg (22%) of **5** as light crystals; mp 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (d, *J* = 6.4 Hz, 2 H), 3.75 (d, *J* = 6.8 Hz, 2 H), 5.10–5.19 (m, 4 H), 5.94–6.14 (m, 2 H), 6.84 (s, 1 H), 7.39 (d, *J* = 2.2 Hz, 1 H), 7.52–7.55 (m, 3 H), 7.91–7.94 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.3, 39.9, 107.6, 116.8, 117.2, 123.3, 124.1, 126.5, 129.3, 129.7, 131.8, 132.3, 135.0, 135.6, 136.8, 137.2, 137.3, 163.2, 179.0. Anal. Calcd for $(C_{21}H_{18}O_2)_2 \cdot H_2O$: C, 81.00, H, 6.15. Found: C, 80.78, H, 5.86.

(18) According to NMR spectroscopy the major side products showed a Pd-mediated rearrangement of the double bond in the allyl group with or without a concomitant Stille coupling in position 6.

(19) **General Procedure for the Heck Reaction in Position 6 – Synthesis of 6,8-Bis(2-methoxycarbonylethenyl)-flavone (6).**
Et_3N (0.04 mL, 0.26 mmol) was added to a suspension of **4** (46 mg, 0.13 mmol), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), methyl acrylate (0.03 mL, 0.33 mmol) and $[P(t\text{-}Bu)_3H]BF_4$ (12 mg, 0.04 mmol) in dioxane (4 mL) under N_2 in a microwave tube. The mixture was heated in a microwave cavity for 30 min at 160 °C. The solution was filtered through Celite® and H_2O (10 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were dried over anhyd $MgSO_4$ before the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel using a manual gradient of CH_2Cl_2–Et_2O (100:0 to 95:5) as eluent to afford 40 mg (79%) of **6** as a white powder; mp 214–215 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 3.87 (s, 3 H), 6.56 (d, *J* = 15.9 Hz, 1 H), 6.71 (d, *J* = 16.4 Hz, 1 H), 6.85 (s, 1 H), 7.56–7.58 (m, 3 H), 7.73 (d, *J* = 15.9 Hz, 1 H), 7.90–7.93 (m, 2 H), 8.01 (d, *J* = 2.2 Hz, 1 H), 8.24 (d, *J* = 16.4 Hz, 1 H), 8.39 (d, *J* = 2.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.0, 52.2, 108.1, 120.2, 122.2, 124.8, 125.6, 126.5, 127.0, 129.5, 131.0, 131.3, 131.6, 132.2, 136.3, 142.3, 154.6, 163.7, 166.8, 166.9, 177.4. Anal. Calcd for $C_{23}H_{18}O_6$: C, 70.76, H, 4.65. Found: C, 70.59, H, 4.74.

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(27) **8-Bromo-6-chloro-3-[3-(*N*-phthalimido)propoxy]-flavone (13).**
A solution of **8** (6.2 g, 17.7 mmol), *N*-(3-bromopropyl)phthalimide (9.5 g, 35.4 mmol) and K_2CO_3 (4.5 g, 35.4 mmol) in DMF (50 mL) was stirred at 50 °C for 15 h. The mixture was allowed to cool and H_2O was added. The solution was acidified with HCl (1 M). The precipitate was filtered off and the solid was recrystallized from EtOH to afford 8.5 g (87%) of **13** as white crystals; mp 185–186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10–2.17 (m, 2 H), 3.83 (t, *J* = 7.0 Hz, 2 H), 4.18 (t, *J* = 6.2 Hz, 2 H), 7.52–7.58 (m, 3 H), 7.70–7.72 (m, 2 H), 7.83–7.85 (m, 2 H), 7.88 (d, *J* = 1.3 Hz, 1 H), 8.14 (d, *J* = 1.3 Hz, 1 H), 8.23–8.25 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.5, 53.5, 70.5, 112.9, 123.4, 124.8, 125.8, 128.9, 129.1, 130.5, 130.9, 131.5, 132.3, 134.1, 136.6, 140.7, 150.5, 156.2, 168.4, 173.5. Anal. Calcd for $C_{26}H_{17}BrClNO_5$: C, 57.96, H, 3.18, N, 2.60. Found: C, 57.79, H, 3.07, N, 2.48.