DOI: 10.1002/ejoc.200901356

Palladium-Catalyzed Direct Arylation of 4-Chromanones: Selective Synthesis of Racemic Isoflavanones and 3,3-Diaryl-4-chromanones

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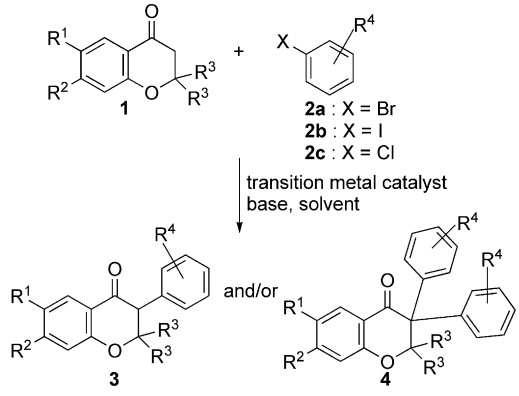
Keywords: Direct arylation / Palladium / C–C coupling / Chromanones / Synthetic methods / Isoflavanones

For the first time, the synthesis of racemic isoflavanones has been achieved in satisfactory to good yields and with high selectivity by Pd-catalyzed direct C-3 arylation of 3-unsubstituted 4-chromanones with aryl bromides with the aid of a $Pd_2(dba)_3$/tBu$_3$PHBF$_4$ catalyst system in the presence of $KHCO_3$ as the base in a dioxane/water mixture (4:1). This catalyst system has also been employed in an unprecedented synthesis of 3,3-diaryl-4-chromanones through direct arylation of 4-chromanones in water.

Introduction

The catalytic direct α-arylation of substrates containing sp^3-hybridized C–H bonds in positions α to a carbonyl group of a ketone, an aldehyde, a carboxylic ester, an azalactone, a lactone, a carboxamide, a lactam, a β-oxo ester, a β-diketone, or ethyl cyanoacetate with aryl halides represents a very useful and convenient tool for efficient formation of Csp^3–Csp^2 bonds with high atom economy.[1] However, no report focusing on transition-metal-catalyzed direct arylation of 4-chromanones **1** at the 3-position with aryl halides **2a**–**c** (Scheme 1) has yet appeared in the literature.



Scheme 1. Transition-metal-catalyzed direct α-arylation of 4-chromanones **1**.

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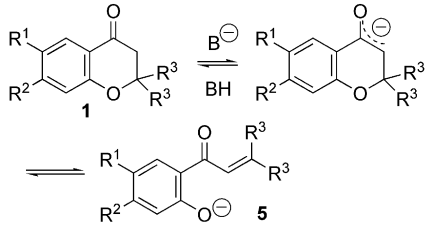
A plausible explanation for the lack of such findings is that compounds**1** might undergo ring-opening to phenolate anions **5**[2] under the strongly basic conditions often required for the catalyzed direct α-arylation of ketones with aryl halides (Scheme 2).[3]



Scheme 2. Base-promoted ring-opening of 4-chromanones.

Moreover, even if it were possible to avoid ring-opening of compounds **1** by use of a weak base, multiple arylation might represent a significant side-reaction,[4] and the direct α-arylation reaction of **1** might produce the required isoflavanones **3** together with a significant amount of the α,α-diarylated derivatives **4**. On the other hand, many of the established procedures for preparation of compounds **3**[5] are severely limited by the use of expensive and/or not readily available starting materials and, in some cases, toxic reagents.

We therefore set out to investigate the Pd-catalyzed direct C-3 arylation of 4-chromanes **1** with aryl bromides **2a** and to develop effective procedures for the selective preparation of racemic isoflavanones **3** and 3,3-diaryl-4-chromanones **4**. The influence of factors such as the nature of the base used in the reactions, the transition metal ligand, the solvent, the **1**/**2a** molar ratio and the reaction temperature was examined.

Results and Discussion

We began our studies by investigating the reaction between 4-chromanone (**1a**) and bromobenzene (**2aa**) in the presence of various Pd precatalysts, ligands, bases and solvents (Table 1). Our attention first focused on the catalyst systems and reaction conditions employed successfully by Buchwald[3c] and Nolan[3j] for the arylation of ketone enolates, so the use of *t*BuONa as the base in toluene[3c] or THF[3j] and catalyst systems consisting of mixtures of $Pd(OAc)_2$ and BINAP[3c] or (SIPr)Pd(allyl)Cl[3j] [SIPr = *N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene] (Entries 1 and 2, Table 1) was examined. However, we found that the resulting reaction mixtures did not contain even traces of either compound **3a** or compound **4a**, nor of unreacted **1a**.

In contrast, the reaction, when performed in a mixture of dioxane/water (4:1) at reflux with K_2CO_3 as the base[6] and a $Pd(OAc)_2$/tBu$_3$PHBF$_4$ catalyst precursor, produced racemic **3a** in 46% isolated yield (Entry 3, Table 1). Interestingly, the selectivity and efficiency of the reaction was increased when $Pd(OAc)_2$ was replaced with $Pd_2(dba)_3$, the **1a**/**2aa** molar ratio now being 1:1.5, as can be seen in Entry 3 in Table 1. In fact, **3a** was isolated in 53% yield from a crude reaction mixture in which the **3a**/**4a** molar ratio was 72:28 (Entry 4, Table 1). On the other hand, the use of a 1:1.1 molar ratio of **1a**/**2aa** allowed us to increase the **3a**/**4ab** molar ratio in the crude reaction mixture further, but the C-3 monoarylated derivative was isolated in only 41% yield (Entry 5, Table 1). Better results were obtained when Na_2CO_3 was employed as the base in place of K_2CO_3 (Entry 6, Table 1). In contrast, $KHCO_3$ gave better results than $NaHCO_3$ in terms of yields and selectivity (Entries 7 and 9, Table 1). The optimal reaction conditions for C-3 monoarylation of **1a** were finally found (Entry 10, Table 1) to involve treatment of this substrate (2.0 equiv.) with **2aa** in a mixture of dioxane/water (4:1) under reflux for 1.2 h in the presence of $KHCO_3$ (2.0 equiv.), $Pd_2(dba)_3$ (2.5 mol-%) and tBu$_3$PHBF$_4$ (10 mol-%). Compound **3a** was thus obtained in 71% isolated yield.

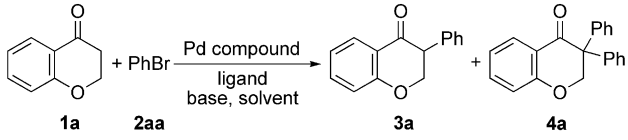
We also observed that the amount of water in the reaction solvent had a significant effect on the selectivity of the C-3 arylation reaction and the yield of racemic **3a**. In fact, the $Pd_2(dba)_3$/tBu$_3$PHBF$_4$-catalyzed reaction between **1a** and **2aa** (1.1 equiv.) in a mixture of dioxane/water (1:1) under reflux in the presence of $KHCO_3$ as the base furnished a 75:25 mixture of racemic **3a**/**4a** from which racemic **3a** was isolated in 45% yield (Entry 11, Table 1). On the other hand, the $Pd_2(dba)_3$/tBu$_3$PHBF$_4$-catalyzed reaction between **1a** and **2aa** (1.1 equiv.) in water under reflux in the presence of $KHCO_3$ provided a mixture of **3a**/**4a** in a 4:96 molar ratio, from which **4a** was isolated in 54% yield (Entry 12, Table 1). Finally, treatment of **1a** with **2aa** (4 equiv.) in water under otherwise the same experimental conditions as Entry 12, Table 1 led us to obtain **4a** with high selectivity and 61% isolated yield (Entry 13, Table 1).[7]

Next, Pd-catalyzed C-3 monoarylation of 4-chromanones **1**, including mono- and trisubstituted derivatives, with a variety of aryl bromides **2a** (Figure 1) under the optimized reaction conditions of Entry 10 of Table 1 was investigated (Table 2).

As shown in Entries 1–9 of Table 2, deactivated, moderately activated and unactivated aryl bromides, including functionalized derivatives, were used, and racemic 3-aryl-4-chromanones **3** were generally obtained with selectivities higher than 90% in satisfactory to good yields.

Notable exceptions were the strongly deactivated 4-bromo-1,2-dimethoxybenzene (**2ag**) (Entry 10, Table 2), which gave the corresponding monoarylated derivative **3k** in only 31% isolated yield, and 1-bromo-4-nitrobenzene

Table 1. Screening of reaction conditions.



Entry	Pd compound [mol-%]	Ligand [mol-%]	Base [equiv.]	**1a**/**2aa** molar ratio	Solvent	Reaction conditions[a] [°C/h]	**3a**, **4a**	Products yield (%)[b]	**3a**/**4a** molar ratio
1	$Pd(OAc)_2$ (10)	(±)-BINAP (12)	*t*BuONa (2.0)	1:2	PhMe	100/2	–	–	–
2	(SIPr)Pd(allyl)Cl (1)		*t*BuONa (1.05)	1:1	THF	50/1	–	–	–
3	$Pd(OAc)_2$ (5)	tBu$_3$PHBF$_4$ (10)	K_2CO_3 (2.0)	1:1.5	dioxane/H_2O (4:1)	reflux/17	**3a**	46	63:37
4	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	K_2CO_3 (2.0)	1:1.5	dioxane/H_2O (4:1)	reflux/17	**3a**	53	72:28
5	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	K_2CO_3 (2.0)	1:1.1	dioxane/H_2O (4:1)	reflux/19	**3a**	41	78:22
6	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	Na_2CO_3 (2.0)	1:1.1	dioxane/H_2O (4:1)	reflux/24	**3a**	47	80:20
7	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	$KHCO_3$ (2.0)	1:1.1	dioxane/H_2O (4:1)	reflux/24	**3a**	58	81:19
8	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	$NaHCO_3$ (2.0)	1:1.1	dioxane/H_2O (4:1)	reflux/24	**3a**	46	75:25
9	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	$KHCO_3$ (2.0)	1.5:1	dioxane/H_2O (4:1)	reflux/2.75	**3a**	63	83:17
10	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	$KHCO_3$ (2.0)	2:1	dioxane/H_2O (4:1)	reflux/1.2	**3a**	71	87:13
11	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	$KHCO_3$ (2.0)	1:1.1	dioxane/H_2O (1:1)	reflux/3.5	**3a**	45	75:25
12	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	$KHCO_3$ (2.0)	1:1.1	H_2O	reflux/24	**4a**	54	4:96
13	$Pd_2(dba)_3$ (2.5)	tBu$_3$PHBF$_4$ (10)	$KHCO_3$ (2.0)	1:4	H_2O	reflux/24	**4a**	61	9:91

[a] The reactions were stopped when the amount of **1a** in the reaction mixture was less than 5% (GLC). [b] Isolated yield.

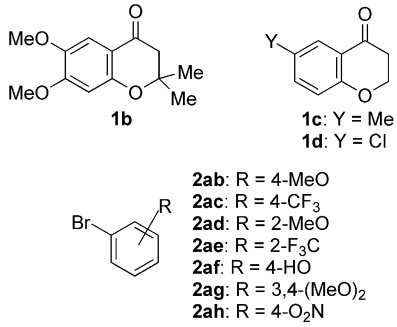


Figure 1. Chemical structures of compounds **1b**–**d** and **2ab**–**2ah**.

Table 2. Pd-catalyzed C-3 arylation of 4-chromanones **1** with aryl bromides **2a**.[a]

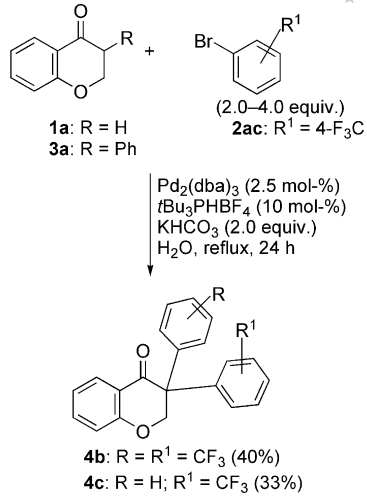
Entry	Reagents		Reaction time [h]	Product[b]	
	1	**2a**		**3**	Yield (%)[c]
1	**1a**	**2ab**	1.10	**3b**	55
2	**1a**	**2ac**	1.15	**3c**	40
3	**1a**	**2ad**	2.20	**3d**	72
4	**1a**	**2ae**	2.20	**3e**	41
5	**1a**	**2af**	2.20	**3f**	44
6	**1b**	**2aa**	22.5	**3g**	73
7	**1c**	**2aa**	2.20	**3h**	81
8	**1d**	**2aa**	2.15	**3i**	58
9	**1c**	**2af**	3.30	**3j**	62
10	**1d**	**2ag**	3.20	**3k**	31
11	**1a**	**2ah**	3.0	**3i**	–

[a] Aryl bromide **2a** (1.0 mmol), 4-chromanone **1** (2.0 mmol), $Pd_2(dba)_3$ (2.5 mol-%), tBu_3PHBF_4 (10 mol-%), $KHCO_3$ (4.0 mmol), dioxane/H_2O (4:1, 5.0 mL). [b] The amount of 3,3-diaryl-4-chromanones **4** in the crude reaction mixtures of Entries 1–10 proved to be less than 10%. [c] Isolated yield.

(**2ah**, Entry 11, Table 2), which afforded no product. Interestingly, the presence of *ortho* substituents in the aryl moieties of compounds **2a** did not hinder the reactions (Entries 3 and 4, Table 2), and the methodology also allowed the coupling of 4-bromophenol (**2af**) with **1a** and **1c** (Entries 5 and 9, Table 2), although only a modest yield was obtained when this bromide was treated with **1a** (Entry 5, Table 2). It is also interesting to point out that the direct arylation involving **1b** required more that 22 h to go to completion (Entry 7, Table 2), probably due to a combination of unfavourable electronic and steric effects.

Finally, we tested the reaction conditions of Entry 13 of Table 1 for the selective synthesis of some representative 3,3-diaryl-4-chromanones other than **4a** by starting from 3-unsubstituted or monosubstituted 4-chromanones.

As shown in Scheme 3, the reaction between **1a** and bromide **2ac** (4 equiv.) in water under reflux for 24 h in the presence of $KHCO_3$ (2 equiv.) and a $Pd_2(dba)_3/tBu_3PHBF_4$ catalyst system led to the required 3,3-diaryl derivative **4b** in 40% yield. Moreover, the reaction between racemic 3-phenyl-4-chromanone (**3a**) and **2ac** (2 equiv.) under the same experimental conditions gave racemic **4c** in 33% yield.



Scheme 3. Pd-catalyzed synthesis of 3,3-diaryl-4-chromanones.

Conclusions

We describe the first examples of Pd-catalyzed direct C-3 arylation of 4-chromanones with aryl bromides. The arylation procedure introduced here, which involves the use of a $Pd_2(dba)_3/tBu_3PHBF_4$ catalyst system and $KHCO_3$ as the base, allows the selective synthesis either of racemic isoflavanones or of 3,3-diaryl-4-chromanones in satisfactory yields, the selectivity of the reaction being dependent both on the reaction solvent and the molar ratio of the reagents.

Our future work will be devoted both to use of the above arylation procedure for the synthesis of naturally occurring racemic isoflavanones possessing significant biological properties[8] and to evaluate the potential for performing asymmetric direct arylation reactions of 3-unsubstituted 4-chromanones with aryl bromides. The use of aryl chlorides and tosylates as alternative electrophiles will be also investigated.

Experimental Section

General Remarks: Melting points are uncorrected. Precoated Merck 60 F_{254} aluminium silica gel sheets were used for TLC analyses. GLC analyses were performed with two types of capillary columns: an Alltech AT-35 bonded FSOT column (30 m × 0.25 mm i.d.) and an Alltech AT-1 bonded FSOT column (30 m × 0.25 mm i.d.). Purifications by flash chromatography were performed with silica gel (Merck 60, particle size 0.040–0.063 mm). EI mass spectra were measured at 70 eV with a GLC/MS system. NMR spectra were recorded at room temperature at 200 (^{1}H), 300 (^{1}H), 50.3 (^{13}C) and 75.5 MHz (^{13}C) and were referenced to TMS. All reactions were performed under argon by standard syringe, cannula and septa techniques. Chroman-4-one (**1a**), 6,7-dimethoxy-2,2-dimethylchroman-4-one (**1b**), 6-methylchroman-4-one (**1c**), 6-chlorochroman-4-one (**1d**), bromobenzene (**2aa**), 4-bromoanisole (**2ab**), 1-bromo-4-(trifluoromethyl)benzene (**2ac**), 2-bromoanisole (**2ad**), 1-bromo-2-(trifluoromethyl)benzene (**2ae**), 4-bromophenol (**2af**), 4-bromo-1,2-dimethoxybenzene (**2ag**), 1-bromo-4-nitrobenzene (**2ah**), $Pd(OAc)_2$, (SIPr)Pd(allyl)Cl, $Pd_2(dba)_3$, (±)-BINAP and tBu_3PHBF_4 were commercially available.

General Procedure for the Pd-Catalyzed Selective C-3 Monoarylation of Chroman-4-ones 1 with Aryl Bromides 2a: A chroman-4-one **1** (2.0 mmol), $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), tBu_3PHBF_4 (29.0 mg, 0.1 mmol), $KHCO_3$ (200 mg, 2.0 mmol) and, if solid, an aryl bromide **2a** (1.0 mmol) were placed in a reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated thrice. A deaerated mixture of dioxane/H_2O (4:1 v/v, 5 mL) and, if liquid, an aryl bromide **2a** (1.0 mmol) were added by syringe, and the stirred mixture was heated at reflux under argon for the period of time given in Tables 1 and 2. After this period of time, the reaction, which was periodically monitored by GLC, GLC-MS and TLC analyses of samples treated with a saturated aqueous NH_4Cl solution and extracted with AcOEt, was complete. The mixture was then allowed to cool to room temperature, diluted with Et_2O (25 mL) and poured into a saturated aqueous NH_4Cl solution (100 mL), and the resulting mixture was extracted with Et_2O (4 × 25 mL). The combined organic extracts were washed with brine, dried and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel and/or by recrystallization. This procedure was employed to prepare 3-arylchroman-4-ones **3a**–**k**.

3-Phenylchroman-4-one (3a): The crude product obtained from the direct C-3 arylation reaction between chroman-4-one (**1a**) and bromobenzene (**2aa**) (Table 1, Entry 8) was purified by flash chromatography on silica gel with use of toluene as eluent. The chromatographic fractions containing compound **3a** were collected and concentrated under reduced pressure. The solid residue was recrystallized from MeOH to give **3a** (159 mg, 71%) as a colourless solid; m.p. 77 °C (ref.[5d] m.p. 77 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.96 (m, 1 H, 5-H), 7.49 (m, 1 H, 7-H), 7.30 (m, 5 H, Ar-H), 7.02 (m, 2 H, 6-H, 8-H), 4.65 (d, J = 7.4 Hz, 2 H, 2-H), 3.98 (t, J = 7.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 192.1, 161.6, 136.0, 135.0, 128.9, 128.6 (2 C), 127.8 (2 C), 127.7, 121.6, 121.0, 117.8, 71.4, 52.3 ppm. EI-MS: m/z (%) = 225 (8) $[M + 1]^+$, 224 (49) $[M]^+$, 120 (100), 104 (35), 103 (10), 92 (26). GLC analysis showed that **3a** was 99% chemically pure. The spectral properties of this compound were in agreement with those previously reported.[9]

3-(4-Methoxyphenyl)chroman-4-one (3b): The crude product obtained from the direct C-3 arylation reaction between chroman-4-one (**1a**) and 4-bromoanisole (**2ab**) (Table 2, Entry 1) was purified by flash chromatography on silica gel with use of a mixture of toluene and AcOEt (95:5 v/v) as eluent to give **3b** (140 mg, 55%) as a yellow solid; m.p. 93–95 °C (ref.[10] m.p. 91–93 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (m, 1 H, 5-H), 7.48 (m, 1 H, 7-H), 7.19 (m, 2 H, Ar-H), 7.00 (m, 2 H, 6-H, 8-H), 6.88 (m, 2 H, Ar-H), 4.62 (m, 2 H, 2-H), 3.93 (t, J = 7.2 Hz, 1 H, 2-H), 3.77 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.4, 161.5, 159.1, 135.9, 129.6 (2 C), 127.7, 126.9, 121.5, 121.0, 117.8, 114.3 (2 C), 71.5, 55.2, 51.5 ppm. EI-MS: m/z (%) = 255 (3) $[M + 1]^+$, 254 (15) $[M]^+$, 135 (10), 134 (100), 119 (13), 92 (4), 91 (9), 65 (4). GLC analysis showed that **3b** was 99% chemically pure. The spectral properties of this compound were in agreement with those previously reported.[10]

3-[4-(Trifluoromethyl)phenyl]chroman-4-one (3c): The crude product obtained from the direct C-3 arylation reaction between chroman-4-one (**1a**) and 1-bromo-4-(trifluoromethyl)benzene (**2ac**) (Table 2, Entry 2) was purified by flash chromatography on silica gel with use of toluene as eluent to give **3c** (117 mg, 40%) as a colourless solid; m.p. 137–139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.96 (dd, J = 8.0, 1.9 Hz, 1 H, 5-H), 7.62 (m, 2 H, Ar-H), 7.53 (m, 1 H, 7-H), 7.42 (m, 2 H, Ar-H), 7.06 (m, 2 H, 6-H, 8-H), 4.68 (m, 2 H, 2-H), 4.07 (t, J = 7.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 191.3, 161.5, 139.0, 136.4, 129.0 (3 C), 128.2, 127.8 (2 C), 125.8, 121.9, 120.8, 117.9, 71.0, 52.0 ppm. EI-MS: m/z (%) = 293 (6) $[M + 1]^+$, 292 (32) $[M]^+$, 172 (6), 151 (5), 121 (9), 120 (100), 103 (5), 92 (34), 64 (6), 63 (5). GLC analysis showed that **3c** was chemically pure. $C_{16}H_{11}F_3O_2$ (292.25): calcd. C 65.76, H 3.79; found C 65.92, H 3.81.

3-(2-Methoxyphenyl)chroman-4-one (3d): The crude product obtained from the direct C-3 arylation reaction between chroman-4-one (**1a**) and 2-bromoanisole (**2ad**) (Table 2, Entry 3) was purified by flash chromatography on silica gel with use of a mixture of toluene and MeCN (98:2 v/v) as eluent to give **3d** (183 mg, 72%) as a viscous, pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (dd, J = 7.8, 1.5 Hz, 1 H, 5-H), 7.44 (m, 1 H, 7-H), 7.26 (m, 1 H, 6-H), 6.98 (m, 5 H, 8-H, Ar-H) 4.68 (m, 1 H, 2-H), 4.62 (m, 1 H, 2-H), 4.48 (dd, J = 10.6, 5.4 Hz, 1 H, 3-H), 4.34 (dd, J = 12.0, 5.4 Hz, 1 H, 3-H), 3.72 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.3, 161.8, 157.3, 135.6, 130.3, 129.0, 127.5, 123.4, 121.5, 121.3, 120.8, 117.8, 111.1, 70.6, 55.4, 48.4 ppm. EI-MS: m/z (%) = 255 (14) $[M + 1]^+$, 254 (75) $[M]^+$, 135 (10), 134 (100), 120 (12), 119 (72), 92 (13), 91 (42). GLC analysis showed that **3d** was 99% chemically pure. The spectroscopic data for this compound were in agreement with those previously reported.[5e]

3-[2-(Trifluoromethyl)phenyl]chroman-4-one (3e): The crude product obtained from the direct C-3 arylation reaction between chroman-4-one (**1a**) and 1-bromo-2-(trifluoromethyl)benzene (**2ae**) (Table 2, Entry 4) was purified by flash chromatography on silica gel with use of toluene as eluent to give **3e** (120 mg, 41%) as a colourless solid; m.p. 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (dd, J = 7.8, 1.5 Hz, 1 H, 5-H), 7.73 (d, J = 7.8 Hz, 1 H, Ar-H), 7.53 (m, 2 H, Ar-H), 7.42 (m, 1 H, 7-H), 7.24 (d, J = 7.5 Hz, 1 H, Ar-H), 7.06 (m, 2 H, 6-H, 8-H), 4.57 (m, 3 H, 2-H, 3-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 191.6, 161.7, 136.2, 133.7, 132.1, 130.7, 127.8, 127.7, 126.3, 126.0, 122.4, 121.7, 121.4, 118.0, 71.8, 49.1 ppm. EI-MS: m/z (%) = 293 (5) $[M + 1]^+$, 292 (39) $[M]^+$, 151 (7), 121 (9), 120 (100), 92 (30), 64 (5). GLC analysis showed that **3e** was chemically pure. $C_{16}H_{11}F_3O_2$ (292.25): calcd. C 65.76, H 3.79; found C 65.88, H 3.80.

3-(4-Hydroxyphenyl)chroman-4-one (3f): The crude product obtained from the direct C-3 arylation reaction between chroman-4-one (**1a**) and 4-bromophenol (**2af**) (Table 2, Entry 5) was purified by flash chromatography on silica gel with use of a mixture of toluene/AcOEt (90:10 v/v) as eluent to give **3f** (106 mg, 44%) as a yellow solid; m.p. 137–140 °C (ref.[2] m.p. 140 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (dd, J = 7.8, 1.7 Hz, 1 H, 5-H), 7.51 (m, 1 H, 7-H), 7.10 (m, 2 H, Ar-H), 7.02 (m, 2 H, 6-H, 8-H), 6.75 (m, 2 H, Ar-H), 5.62 (br. s, 1 H, OH), 4.62 (m, 2 H, 2-H), 3.94 (dd, J = 8.7, 6.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.0, 161.9, 155.7, 136.5, 129.9 (2 C), 127.1, 126.4, 121.7, 121.0, 118.0, 116.1 (2 C), 71.7, 51.7 ppm. EI-MS: m/z (%) = 293 (5) $[M + 1]^+$, 292 (39) $[M]^+$, 151 (7), 121 (9), 120 (100), 92 (30), 64 (5). GLC analysis showed that **3f** was 99% chemically pure. The spectroscopic data for this compound were in agreement with those previously reported.[9]

6,7-Dimethoxy-2,2-dimethyl-3-phenylchroman-4-one (3g): The crude product obtained from the direct C-3 arylation reaction between 6,7-dimethoxy-2,2-dimethylchroman-4-one (**1b**) and 1-bromobenzene (**2aa**) (Table 2, Entry 6) was purified by flash chromatography on silica gel with use of a mixture of toluene and AcOEt (80:20 v/v) as eluent to give **3g** (228 mg, 73%) as a pale yellow solid; m.p. 170–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (m, 6 H, 5-H, Ar-H), 6.49 (s, 1 H, 8-H), 3.94 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3),

3.60 (s, 1 H, 3-H), 1.49 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 191.1, 156.5, 155.8, 144.3, 135.6, 129.4 (2 C), 128.6 (2 C), 127.5, 112.0, 107.1, 100.6, 81.8, 62.0, 56.2, 56.1, 26.7, 24.7 ppm. EI-MS: *m*/*z* (%) = 313 (16) $[M + 1]^+$, 312 (73), 298 (11), 297 (53), 181 (74), 180 (100), 165 (17), 137 (11), 117 (13), 91 (9). GLC analysis showed that **3g** was chemically pure. $C_{19}H_{20}O_4$ (312.36): calcd. C 73.06, H 6.45; found C 73.22, H 6.47.

6-Methyl-3-phenylchroman-4-one (3h): The crude product obtained from the direct C-3 arylation reaction between 6-methylchroman-4-one (**1c**) and 1-bromobenzene (**2aa**) (Table 2, Entry 7) was purified by flash chromatography on silica gel with use of a mixture of toluene and AcOEt (98:2 v/v) as eluent to give **3h** (193 mg, 81%) as a pale yellow solid; m.p. 42–43 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.70 (s, 1 H, 5-H), 7.24 (m, 6 H, 7-H, Ar-H), 6.86 (d, *J* = 8.4 Hz, 1 H, 8-H), 4.53 (d, *J* = 7.2 Hz, 2 H, 2-H), 3.87 (t, *J* = 7.2 Hz, 1 H, 3-H), 2.24 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.1, 159.5, 136.9, 135.2, 130.8, 128.7, 128.5 (2 C), 127.5 (2 C), 127.1, 120.5, 117.5, 71.3, 52.2, 20.3 ppm. EI-MS: *m*/*z* (%) = 239 (9) $[M + 1]^+$, 238 (48) $[M]^+$, 135 (10), 134 (100), 106 (14), 105 (12), 78 (15), 77 (9). GLC analysis showed that **3h** was chemically pure. $C_{16}H_{14}O_2$ (238.28): calcd. C 80.65, H 5.92; found C 80.94, H 5.93.

6-Chloro-3-phenylchroman-4-one (3i): The crude product obtained from the direct C-3 arylation reaction between 6-chlorochroman-4-one (**1d**) and 1-bromobenzene (**2aa**) (Table 2, Entry 8) was purified by flash chromatography on silica gel with use of toluene as eluent to give **3i** (151 mg, 58%) as a pale yellow solid; m.p. 99–101 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 2.6 Hz, 1 H, 5-H), 7.33 (m, 6 H, 7-H, Ar-H), 6.96 (d, *J* = 8.8 Hz, 1 H, 8-H), 4.65 (d, *J* = 7.2 Hz, 2 H, 2-H), 3.96 (t, *J* = 7.2 Hz, 1 H, 3-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 191.0, 160.0, 135.8, 134.5, 128.9, 128.5 (2 C), 127.9 (2 C), 127.1, 126.9, 121.8, 119.6, 71.5, 51.9 ppm. EI-MS: *m*/*z* (%) = 259 (11) $[M + 1]^+$, 258 (49) $[M]^+$, 156 (32), 155 (9), 154 (100), 126 (19), 104 (55), 103 (15), 78 (11), 63 (10). GLC analysis showed that **3i** was chemically pure. $C_{15}H_{11}ClO_2$ (258.70): calcd. C 69.64, H 4.29; found C 69.87, H 4.31.

3-(4-Hydroxyphenyl)-6-methylchroman-4-one (3j): The crude product obtained from the direct C-3 arylation reaction between 6-methylchroman-4-one (**1c**) and 4-bromophenol (**2af**) (Table 2, Entry 9) was purified by flash chromatography on silica gel with use of a mixture of toluene/AcOEt (85:15 v/v) as eluent to give **3j** (158 mg, 62%) as a viscous, pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 1.7 Hz, 1 H, 5-H), 7.31 (dd, *J* = 1.7, 8.4 Hz, 1 H, 7-H), 7.03 (m, 2 H, Ar-H), 6.90 (d, *J* = 8.4 Hz, 1 H, 8-H), 6.70 (m, 2 H, Ar-H), 4.56 (m, 2 H, 2-H), 3.89 (dd, *J* = 9.0, 6.0 Hz, 1 H, 3-H), 2.30 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 194.1, 160.0, 155.7, 137.6, 131.2 (2 C), 129.8, 127.4, 126.6, 120.6, 117.8 (2 C), 116.1, 71.7, 51.8, 20.5 ppm. EI-MS: *m*/*z* (%) = 255 (18) $[M + 1]^+$, 254 (100) $[M]^+$, 253 (26), 239 (29), 225 (39), 207 (49), 135 (54), 119 (51), 108 (20), 91 (16), 79 (21), 44 (19). GLC analysis showed that **3j** was chemically pure. $C_{16}H_{14}O_3$ (254.28): calcd. C 75.57, H 5.55; found C 75.74, H 5.56.

6-Chloro-3-(3,4-dimethoxyphenyl)chroman-4-one (3k): The crude product obtained from the direct C-3 arylation reaction between 6-chlorochroman-4-one (**1d**) and 4-bromo-1,2-dimethoxybenzene (**2ag**) (Table 2, Entry 10) was purified by flash chromatography on silica gel with use of a mixture of toluene/AcOEt (90:10 v/v) as eluent to give **3k** (98 mg, 31%) as a yellow solid; m.p. 106–108 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 2.7 Hz, 1 H, 5-H), 7.43 (dd, *J* = 8.9, 2.7 Hz, 1 H, 7-H), 6.97 (d, *J* = 8.9 Hz, 1 H, 8-H), 6.83 (m, 2 H, Ar-H), 6.77 (s, 1 H, Ar-H), 4.66 (d, *J* = 7.1 Hz, 2 H, 2-H), 3.92 (t, *J* = 7.1 Hz, 1 H, 3-H), 3.86 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3) ppm. EI-MS: *m*/*z* (%) = 319 (5) $[M + 1]^+$, 318 (30) $[M]^+$, 165 (11), 164 (100), 149 (17), 91 (6), 77 (6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 191.3, 160.0, 149.3, 148.9, 135.9, 127.2, 126.8, 121.7, 120.7, 119.7, 111.8 (2 C), 111.6, 71.6, 56.0 (2 C), 51.6 ppm. GLC analysis showed that **3k** was chemically pure. $C_{17}H_{15}ClO_4$ (318.75): calcd. C 64.06, H 4.74; found C 64.25, H 4.76.

3,3-Diphenylchroman-4-one (4a, Entry 13, Table 1): Chroman-4-one (**1a**, 148 mg, 1.0 mmol), $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), tBu$_3$PHBF$_4$ (29.0 mg, 0.1 mmol) and $KHCO_3$ (200 mg, 2.0 mmol) were placed in a reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and backfilled with argon, and this sequence was repeated thrice. Deaerated water (5 mL) and 4-bromobenzene (**2aa**, 0.42 mL, 628 mg, 4.0 mmol) were added by syringe, and the mixture was stirred under reflux under argon for 24 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (25 mL) and poured into a saturated aqueous NH_4Cl solution (100 mL), and the resulting mixture was extracted with Et_2O (4 × 25 mL). The combined organic extracts were dried and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel with use of a mixture of toluene/petroleum ether (60:40 v/v) as eluent to give **4a** (183 mg, 61%) as a pale yellow solid; m.p. 128–130 °C (ref.[5d] m.p. 129–131 °C). ^1H NMR (200 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 7.6, 1.8 Hz, 1 H, 5-H), 7.39 (m, 1 H, 7-H), 7.28 (m, 10 H, Ar-H), 6.95 (m, 2 H, 6-H, 8-H), 4.88 (s, 2 H, 2-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 193.2, 160.6, 138.4 (2 C), 135.8, 128.8 (4 C), 128.5 (4 C), 128.3, 127.7 (2 C), 121.4, 121.0, 117.6, 73.8, 59.5 ppm. EI-MS: *m*/*z* (%) = 301 (8) $[M + 1]^+$, 300 (33) $[M]^+$, 223 (17), 181 (16), 180 (100), 179 (37), 178 (28), 165 (45). GLC analysis showed that **4a** was chemically pure. $C_{21}H_{16}O_2$ (300.35): calcd. C 83.98, H 5.37; found C 84.49, H 5.39.

3,3-Bis[4-(trifluoromethyl)phenyl]chroman-4-one (4b): Chroman-4-one (**1a**, 148 mg, 1.0 mmol), $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), tBu$_3$PHBF$_4$ (29.0 mg, 0.1 mmol) and $KHCO_3$ (200 mg, 2.0 mmol) were placed in a reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and backfilled with argon, and this sequence was repeated thrice. Deaerated water (5 mL) and 1-bromo-4-(trifluoromethyl)benzene (**2ac**, 0.56 mL, 900 mg, 4.0 mmol) were added by syringe, and the mixture was stirred under reflux under argon for 24 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (25 mL) and poured into a saturated aqueous NH_4Cl solution (100 mL), and the resulting mixture was extracted with Et_2O (4 × 25 mL). The combined organic extracts were dried and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel with use of a mixture of toluene/petroleum ether (20:80 v/v) as eluent to give **4b** (175 mg, 40%) as a colourless solid; m.p. 115–117 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 7.8, 1.7 Hz, 1 H, 5-H), 7.60 (m, 4 H, Ar-H), 7.48 (m, 1 H, 7-H), 7.39 (m, 4 H, Ar-H), 7.01 (m, 2 H, 6-H, 8-H), 4.90 (s, 2 H, 2-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 191.9, 160.5, 141.9 (2 C), 136.6, 129.3 (6 C), 128.4 (4 C), 126.6, 125.7 (2 C), 122.0, 121.2, 120.5, 117.8, 73.4, 59.4 ppm. EI-MS: *m*/*z* (%) = 437 (3) $[M + 1]^+$, 436 (11) $[M]^+$, 417 (8), 297 (6), 247 (6), 227 (6), 178 (10), 121 (9), 120 (100), 92 (23). GLC analysis showed that **4b** was chemically pure. $C_{23}H_{14}F_6O_2$ (436.35): calcd. C 63.31, H 3.23; found C 63.68, H 3.24.

3-Phenyl-3-[4-(trifluoromethyl)phenyl]chroman-4-one (4c): 3-Phenylchroman-4-one (**3a**, 224 mg, 1.0 mmol), $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol), tBu$_3$PHBF$_4$ (29.0 mg, 0.1 mmol) and $KHCO_3$

(200 mg, 2.0 mmol) were placed in a reaction vessel under a stream of argon. The reaction vessel was fitted with a silicon septum, evacuated and back-filled with argon, and this sequence was repeated thrice. Deaerated water (5 mL) and 1-bromo-4-(trifluoromethyl)-benzene (**2ac**, 0.28 mL, 450 mg, 2.0 mmol) were added by syringe, and the mixture was stirred at reflux under argon for 24 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (25 mL) and poured into a saturated aqueous NH_4Cl solution (100 mL), and the resulting mixture was extracted with Et_2O (4 × 25 mL). The combined organic extracts were dried and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel with use of a mixture of toluene and petroleum ether (60:40 v/v) as eluent to give **4c** (122 mg, 33%) as a colourless solid; m.p. 151–153 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.02 (dd, J = 8.0, 1.8 Hz, 1 H, 5-H), 7.57 (m, 2 H, Ar-H), 7.36 (m, 10 H, 7-H, Ar-H), 6.98 (m, 2 H, 6-H, 8-H), 4.89 (s, 1 H, 2-H), 4.88 (s, 1 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.5, 160.6, 142.7, 137.6, 136.1, 129.3 (2 C), 128.71 (2 C), 128.67, 128.3 (2 C), 128.1, 125.8 (2 C), 125.4, 122.2, 121.7, 120.8, 117.7, 73.6, 59.4 ppm. EI-MS: m/z (%) = 369 (7) $[M + 1]^+$, 368 (28) $[M]^+$, 291 (12), 248 (48), 233 (13), 223 (13), 179 (26), 178 (27), 120 (100), 92 (20). GLC analysis showed that **4c** was chemically pure. $C_{22}H_{15}F_3O_2$ (368.35): calcd. C 71.74, H 4.10; found C 72.36, H 4.12.

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Received: November 24, 2009
Published Online: January 28, 2010

