Synthesis of Functionalized 2′,4-Diarylbenzophenones Based on Site-Selective Suzuki Cross-Coupling Reactions

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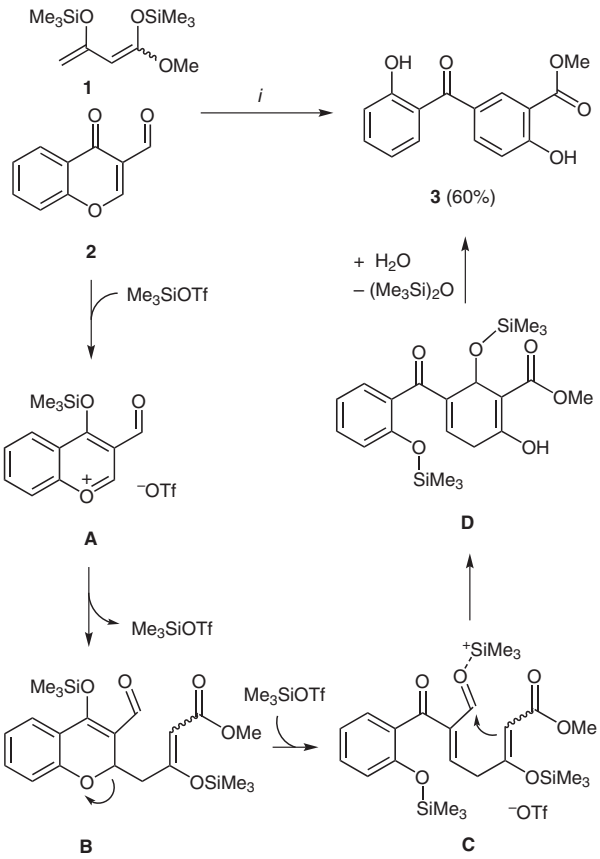
Abstract: The palladium(0)-catalyzed Suzuki cross-coupling reaction of the bis(triflates) of 2′,4-dihydroxybenzophenones afforded 2′,4-diarylbenzophenones. The reactions proceeded with very good site selectivity. The first attack occurred at carbon atom C-4.

Key Words: benzophenones, cross coupling, palladium, site selectivity, Suzuki reaction

4-Arylbenzophenones possess a wide range of pharmacological properties. This includes, for example, cytotoxic[1] and antibacterial activity,[2] inhibition of ^{3}H-progesterone binding,[3] inhibition of the interleukin (IL-1) biosynthesis,[4] inhibition of the human type-2 steroid 5α-reductase,[5] inhibition of COX-1,[6] and inhibition of human liver microsomes.[7] 2-Benzoylfluorenones and 2-benzoylfluorenes, which are structurally related to 4-arylbenzophenones, also represent pharmacologically relevant entities.[8] The 4-arylbenzophenone core structure is present, albeit hidden in a polycyclic framework, in various naturally occurring anthraquinones and tetracyclins.[9] Microtubules represent an important target for anticancer therapy. The benzophenone phenstatin, 2-hydroxy- and 2-aminobenzophenones act as antitubulin agents.[10,11] We have reported that 4-(2-hydroxybenzoyl)salicylic acids show a good in vitro activity in a selectin bioassay.[12] Functionalized benzophenones are also widely used as photosensitizers[13] and UV filters.[14]

Classic syntheses of benzophenones rely on reactions of aryllithium or magnesium reagents with aldehydes and subsequent oxidation and on Friedel–Crafts acylations.[11a,15] For the synthesis of functionalized benzophenones (e.g. containing a hydroxy, halide or ester group), these methods often give unsatisfactory results, due to competing side reactions. Therefore, the development of alternative methods is of considerable interest.[16] Recently, we have reported[12] a new approach to 4-(2-hydroxybenzoyl)salicylates by domino 'Michael–retro-Michael–Mukaiyama–aldol' reactions of 3-formylchromones with 1,3-bis(silyloxy)-1,3-butadienes. Herein, we report the synthesis of 2′,4-diarylbenzophenones based on what are, to the best of our knowledge, the first palladium(0)-catalyzed Suzuki cross-coupling reactions of bis(triflates) of 2′,4-dihydroxybenzophenones. These reactions proceed with very good site-selectivity.[17] The products, functionalized 4-arylbenzophenones and 2′,4-diarylbenzophenones, are not readily available and have only scarcely been reported in the literature so far.

The TMSOTf-mediated reaction of 3-formylchromone (**2**) with 1,3-bis(trimethylsilyloxy)buta-1,3-diene (**1**) afforded the 2′,4-dihydroxybenzophenone **3**.[12] Its formation can be explained by a domino 'addition–retro-Michael–Mukaiyama–aldol' reaction (Scheme 1).



Scheme 1 Synthesis of **3**. *Reagents and conditions*: (i) 1. **2** (1.0 equiv), Me_3SiOTf (0.3 equiv), CH_2Cl_2, 0 °C; 2. **1** (1.1 equiv), 0 °C → 20 °C, 12 h; 3. HCl (10%).

2′,4-Dihydroxybenzophenone **3** was transformed into the bis(triflate) **4** in 84% yield (Scheme 2). The Suzuki reaction of **4** with boronic acids **5a–j** afforded the novel 2′,4-diarylbenzophenones **6a–j** in good yields (Scheme 2,

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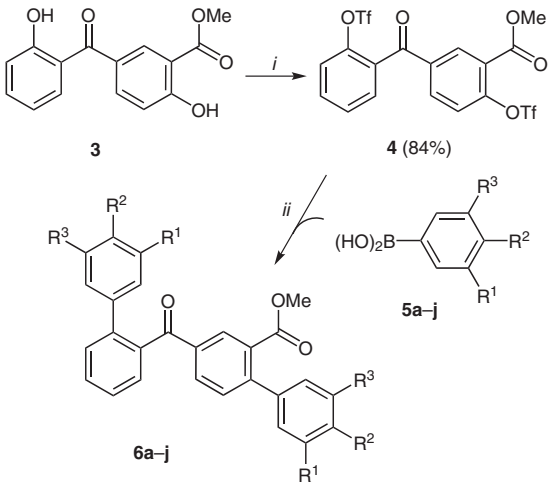
Table 1). The best yields were obtained when $Pd(PPh_3)_4$ (3 mol%) was used as the catalyst, when 2.6 equivalents of the boronic acid were employed, and when the reaction was carried out in 1,4-dioxane (reflux, 4 h) using K_3PO_4 as the base.[18,19]



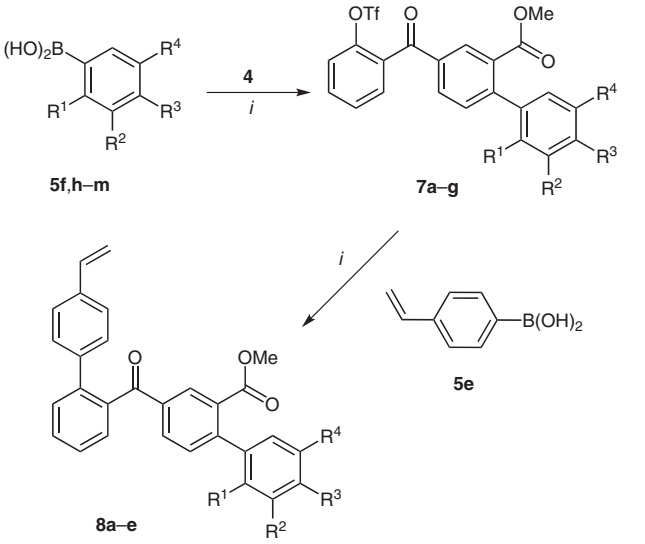
Scheme 2 Synthesis of **6a–j**. *Reagents and conditions*: (i) 1. **3** (1.0 equiv), pyridine (4.0 equiv), CH_2Cl_2, –78 °C, 10 min; 2. Tf_2O (2.4 equiv), –78 °C → 0 °C, 4 h; (ii) **4** (1.0 equiv), **5a–j** (2.6 equiv), K_3PO_4 (3.0 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 110 °C, 4 h.

Table 1 Synthesis of **6a–j**

5,6	R^1	R^2	R^3	Yield[a] (%) of **6**
a	H	Me	H	87
b	H	H	H	82
c	H	Et	H	56
d	Cl	H	H	77
e	H	vinyl	H	80
f	H	Cl	H	46
g	H	Br	H	65
h	OMe	OMe	H	62
i	H	OH	H	67
j	OMe	OMe	OMe	50

[a] Yields of isolated products.

The Suzuki reaction of **4** with one equivalent of boronic acids **5f** and **5h–m** afforded the 4-arylbenzophenones **7a–g** with very good site-selectivity (Scheme 3, Table 2).[18,20] The remaining triflate group of **7a**,**c**,**e–g**, located at carbon atom C-2′, could be further reacted with boronic acid **5e** to give the 2′,4-diarylbenzophenones **8a–e** containing two different aryl groups (Scheme 3, Table 3). The configurations of all products were studied by spectroscopic methods. The structures of some derivatives were independently confirmed by X-ray crystal structure analyses.



Scheme 3 Synthesis of **7a–g**. *Reagents and conditions*: (i) **4** (1.0 equiv), **5f**,**h–m** (1.3 equiv), K_3PO_4 (3.0 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 110 °C, 4 h; (ii) **7a**,**c**,**e–g** (1.0 equiv), **5e** (1.3 equiv), K_3PO_4 (3.0 equiv), $Pd(PPh_3)_4$ (3 mol%), 1,4-dioxane, 110 °C, 4 h.

Table 2 Synthesis of **7a–g**

5	7	R^1	R^2	R^3	R^4	Yield[a] (%) of **7**
k	**a**	H	Me	H	Me	78
f	**b**	H	H	Cl	H	45
l	**c**	OEt	H	H	H	89
m	**d**	Br	H	H	H	78
h	**e**	H	OMe	OMe	H	44
i	**f**	H	H	OH	H	63
j	**g**	H	OMe	OMe	OMe	43

[a] Yields of isolated products.

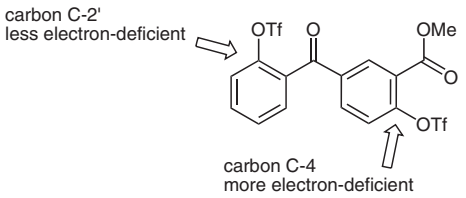
Table 3 Synthesis of **8a–e**

7	8	R^1	R^2	R^3	R^4	Yield[a] (%) of **8**
a	**a**	H	Me	H	Me	60
f	**b**	H	H	OH	H	55
c	**c**	H	H	H	H	65
e	**d**	H	OMe	OMe	H	62
g	**e**	H	OMe	OMe	OMe	44

[a] Yields of isolated products.

The site-selective formation of products **7a–g** might be explained by the fact that the oxidative addition of palladium usually occurs first at the most electron-deficient carbon atom (Scheme 4).[17] Carbon atom C-4 is expected to be more electron deficient than C-2′. One electron-withdrawing benzoyl group is located *ortho* to C-2′. In contrast, both an electron-withdrawing benzoyl group and

an electron-withdrawing ester group are located *para* and *ortho* to C-4, respectively. In addition, it might also play a role that carbon C-2′ is more sterically hindered than C-4.



Scheme 4 Possible explanation for the site-selective formation of products **7a–g**

In conclusion, we have reported the synthesis of 2′,4-diarylbenzophenones based on what are, to the best of our knowledge, the first palladium(0)-catalyzed Suzuki cross-coupling reactions of bis(triflates) of 2′,4-dihydroxybenzophenones. These reactions proceed with very good site-selectivity.

Acknowledgment

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(17) For a review of site-selective palladium(0)-catalyzed cross-coupling reactions, see: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.
(18) **Typical Procedure for the Synthesis of 6a–j**: A 1,4-dioxane solution (5 mL/mmol of **4**) of **5a–j**, K_3PO_4, $Pd(PPh_3)_4$ and **4** was stirred at 110 °C for 4 h. After cooling to 20 °C, a sat. aq solution of NH_4Cl was added, the organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography.
(19) **Methyl 4′-Methyl-4-(4′-methylbiphenylcarbonyl)-biphenyl-2-carboxylate (6a)**: Starting with **4** (220 mg, 0.4 mmol), K_3PO_4 (261 mg, 1.2 mmol), $Pd(PPh_3)_4$ (3 mol%), *p*-tolylboronic acid (144 mg, 1.1 mmol) and 1,4-dioxane (2 mL), **6a** was isolated as a highly viscous oil (200 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 3.56 (s, 3 H, OCH_3), 6.95 (d, 2 H, *J* = 8.0 Hz, ArH), 7.04–7.21 (m, 6 H, ArH), 7.35–7.53 (m, 5 H, ArH), 7.70 (dd, 1 H, *J* = 1.9, 8.0 Hz, ArH), 7.98 (d, 1 H, *J* = 1.9 Hz, ArH). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 21.0 (CH_3), 21.2 (CH_3), 52.1 (OCH_3), 126.9 (4 × C, CH), 127.9, 128.8, 128.9 (CH), 129.0 (4 × C, CH), 130.2, 130.6, 131.4, 132.1 (CH), 135.8 (2 × C), 137.1 (C), 137.2 (2 × C), 137.7, 138.3, 141.3, 146.3, 168.4 (C), 197.4 (C=O). IR (KBr): 3080, 3057, 3025 (w), 1724, 1659 (s), 1613 (w), 1595 (m), 1574, 1518 (w), 1438, 1310, 1277 (m), 1231 (s), 1152, 1082, 972 (m), 819, 704 (s), 536 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 420 (100) [M$^+$], 405 (21), 373 (09), 359 (23), 332 (07), 253 (26), 210 (07), 195 (40), 165 (39), 152 (25). HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{29}H_{24}O_3$: 420.17200; found: 420.17153.
(20) **Methyl 2′-Bromo-4-[2-(trifluoromethylsulfonyloxy)-benzoyl]biphenyl-2-carboxylate (7d)**: Starting with **4** (150 mg, 0.3 mmol), K_3PO_4 (171 mg, 0.8 mmol), $Pd(PPh_3)_4$ (3 mol%), 2-bromophenylboronic acid (65 mg, 0.3 mmol) and 1,4-dioxane (2 mL), **7d** was isolated as a highly viscous oil (120 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.58 (s, 3 H, OCH_3), 7.13–7.17 (m, 2 H, ArH), 7.28–7.39 (m, 3 H, ArH), 7.43–7.48 (m, 1 H, ArH), 7.54–7.62 (m, 3 H, ArH), 7.94 (dd, 1 H, *J* = 2.1, 8.0 Hz, ArH), 8.36 (d, 1 H, *J* = 2.1 Hz, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 52.3 (OCH_3), 122.7, 127.1, 128.3, 129.2, 129.7, 129.8, 131.3, 131.8, 132.3, 132.9, 133.2 (CH), 134.6, 134.9, 135.0, 136.0, 141.5, 146.7, 146.8, 147.2, 166.2 (C), 191.4 (C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.29 (CF). IR (KBr): 3053, 2953, 2923 (w), 1728, 1672 (s), 1567 (m), 1482 (w), 1309, 1294 (m), 1241, 1203 (s), 1168 (m), 1087 (s), 948 (m), 887, 769, 592 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 544 (100) [M$^+$], 331 (12), 301 (48), 271 (24), 242 (75), 215 (7), 183 (5), 151 (11), 69 (15). HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{22}H_{14}BrF_3O_6S$: 544.17200; found: 544.171525.