DOI: 10.1002/ejoc.200900581

An Economical Access to 3,4-Diaryl-2(5*H*)-furanones and 4-Aryl-6-methyl-2(2*H*)-pyranones by Pd-Catalyzed Suzuki-Type Arylation of 3-Aryl-4-tosyloxy-2(5*H*)-furanones and 6-Methyl-4-tosyloxy-2(2*H*)-pyranones, Respectively

Fabio Bellina,*[a] Chiara Marchetti,[a] and Renzo Rossi*[a]

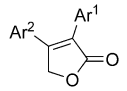
Keywords: Synthetic methods / C–C coupling / Palladium / Cross-coupling / Heterocycles

Both symmetrical and unsymmetrical 3,4-diaryl-substituted 2(5*H*)-furanones have been efficiently synthesized using an inexpensive procedure involving the $Pd(OAc)_2/PCy_3$-catalyzed Suzuki-type arylation of readily available 3-aryl-4-tosyloxy-2(5*H*)-furanones as the key step. The mild conditions of this arylation protocol have also been used for the high yielding synthesis of 4-aryl-6-methyl-2(2*H*)-pyranones from 6-methyl-4-tosyloxy-2(2*H*)-pyranone.

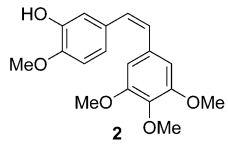
Introduction

Five-membered heterocycles with two aryl groups on adjacent positions include a very large number of biologically active compounds[1] such as cyclooxygenase-2 (COX-2) inhibitors,[2] anticoccidial agents,[3] cannabinoid CB_1 receptor antagonists,[4] ligands for the Niemann Pick C1 Like 1 (NPC1L1) protein,[5] antagonists for the human CCK_1 receptor,[6] inhibitors of transforming growth factor-beta,[7] p38α MAP kinase,[8] and HMG-CoA reductase,[9] and substances with potent cytotoxic activity against human cancer cell lines.[10]

Among these heterocycles, unsymmetrical 3,4-diaryl-substituted 2(5*H*)-furanones **1** represent a class of compounds that has received considerable attention because of their biological properties. One of these compounds is Rofecoxib (Vioxx®) (**1a**) (Figure 1), a COX-2 inhibitor,[11] which was withdrawn from the market in 2004 following the detection of an increase in cardiovascular events.[12] Additional bioactive diaryl-substituted heterocycles of this class include compound **1b**[10h] and **1c**[10f] (Figure 1), which are (*Z*)-restricted analogues of combretastatin A-4 (**2**) (Figure 1), a potent inhibitor of tubulin polymerization which displays potent cytotoxic activity against a variety of tumor cell lines and tumors.[1a,1c,13] Compound **1b** proved to be more cytotoxic than **2** against the NCI 60 human tumor cell lines panel[10h] and **1c** was shown to be remarkably potent in all tested tumor cell lines and strongly inhibited tubulin polymerization at doses as low as 1 mM.[10f] Thus, a number of methods have been developed for the synthesis of compounds **1**.[10g,10k,14] However, these methods are limited by the use of not readily available starting materials,[10j,14a,14b] toxic reagents and synthetic intermediates,[14c,14e] multiple palladium-catalyzed cross-coupling reactions,[10g,14c,14e,14f] or a very large molar excess of Grignard reagents.[14d] Therefore, we recently decided to develop a new procedure for accessing compounds **1** from commercially available starting materials via a chemistry free from the above mentioned limitations, involving Suzuki-type reactions of 3-aryl-4-tosyloxy-2(5*H*)-furanones **3**, a class of activated tosylates, with arylboronic acids **4** as a key step.



1a: Ar^1 = Ph; Ar^2 = 4-$MeSO_2C_6H_4$
1b: Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 2-naphthyl
1c = Ar^1 = 3,4,5-$(MeO)_3C_6H_2$; Ar^2 = 3-NH_2,4-$MeOC_6H_3$•HCl



2

Figure 1. Chemical structures of compounds **1a**–**c** and **2**.

In this paper we provide an account on the results of this investigation. Moreover, we describe that the protocol developed for efficiently performing the cross-coupling between **3** and **4** was also successfully used for the preparation of a variety of 4-aryl-6-methyl-2(2*H*)-pyranones **6** from the corresponding 4-tosylate **5** (Figure 2).

[a] Dipartimento di Chimica e Chimica Industriale, University of Pisa,
Via Risorgimento 35, 56126 Pisa, Italy
Fax: +39-0502219260
E-mail: bellina@dcci.unipi.it
rossi@dcci.unipi.it
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900581.

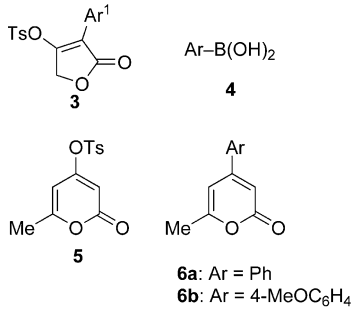
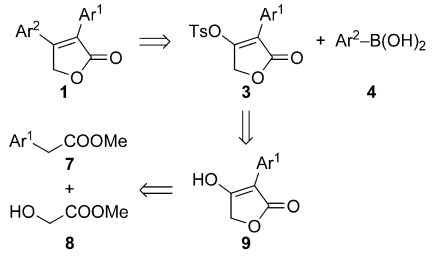


Figure 2. Chemical structures of compounds **3**, **4**, **5** and **6a**,**b**.

It should be noted that, recently, it has been reported that some compounds of type **6** show antimicrobial activity.[15] In particular, **6a** was found to exhibit promising inhibitory activity against *Fusarium oxysporum* and **6b** demonstrated modest inhibitory activity against *Scizosaccharomyces pombi*.[15]

Results and Discussion

We planned the synthesis of compounds **1** according to the retrosynthetic sequence illustrated in Scheme 1 in which commercially available methyl arylacetates **7** and methyl hydroxyacetate (**8**) were the starting materials.



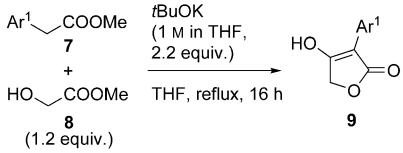
Scheme 1. Retrosynthesis of compounds **1**.

Thus, a tandem process, which combines a transesterification and a subsequent Dieckmann condensation was employed to prepare 3-aryltetronic acids **9** from **7** and **8** according to a procedure very recently reported in the literature.[16] As shown in Table 1, treatment of methyl arylacetates **7a**–**c** with 1.2 equiv. of **8** in refluxing THF in the presence of 2.2 equiv. of *t*BuOK gave compounds **9a**–**c** in 50–63% yield.

Compounds **9a**, **9b** and **9c** were then reacted with 1.05 equiv. of *p*-toluenesulfonyl chloride in CH_2Cl_2 at room temperature in the presence of 1.2 equiv. of Et_3N to provide the corresponding 4-tosylate derivatives, **3a**, **3b** and **3c** in 77, 82 and 75% yield, respectively.

The possibility of using tosylates **3a**–**c** as activated electrophiles in efficient transition metal-catalyzed arylation reactions with arylboronic acids **4** was next evaluated.[17–19] Since a large variety of arylboronic acids are commercially available and potassium aryltrifluoroborates show, in general, lower reactivity[20] and are more expensive than the corresponding boronic acids, which are often employed as starting materials for the synthesis of these salt,[21] we preferred to use arylboronic acids as organometallic partners of the Suzuki-type cross-coupling reactions.

Table 1. Synthesis of 3-aryltetronic acids **9a**–**c**.



Entry	7	Ar^1	9	Yield (%)
1	**7a**	Ph	**9a**	63
2	**7b**	3,4,5-$(MeO)_3C_6H_2$	**9b**	50
3	**7c**	4-$CF_3C_6H_4$	**9c**	53

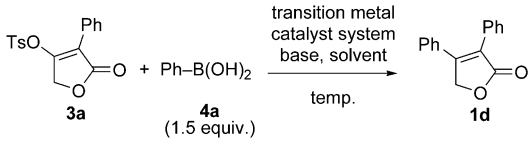
Thus, a set of experiments was performed using **3a** and phenylboronic acid (**4a**) as model substrates. As shown in Table 2, a variety of catalyst systems, bases and solvents were screened for the reaction of **3a** with **4a**.

This screening was necessary as it has previously been reported that the $PdCl_2(PPh_3)_2$-catalyzed reaction of **3a** with arylboronic acids in THF at 60 °C in the presence of an aqueous solution of KF as the base gives only a trace amount of the required arylated products.[18e]

At first, we obtained a very disappointing result when the reaction of **3a** with 1.5 equiv. of **4a** was performed under experimental conditions very similar to those successfully employed by Wu, Zhang and Gao[17b] for the reaction of 4-tosyloxy-2(5*H*)-furanone with arylboronic acids, i.e. using a $RhCl(PPh_3)_2$/dppf catalyst system and CsF as base in a mixture of toluene and water (Table 2, entry 1). An unsatisfactory result was also obtained when the reaction of **3a** with **4a** was carried out under experimental conditions (Table 2, entry 2) similar to those used by Zhang and coworkers[14f] for the Suzuki-type arylation of halogenated 2(5*H*)-furanones. However, better results were obtained when diphosphanes with a wide bite angle, such as dppf (Table 2, entry 3) or Xantphos (Table 2, entry 4), were employed as ancillary ligands for palladium in place of PPh_3. On the contrary, the use of (*S*)-BINAP, which has a bite angle (93°) lower than those of dppf and Xantphos (99° and 111°, respectively),[22] led to the formation of traces of the required derivative **1d** (Table 2, entry 5).

In searching for milder and efficient reaction conditions than those above summarized, we decided to perform the reaction between **3a** and **4a** in methanol at 60 °C using a catalyst system consisting of a 1:2 mixture of $Pd(OAc)_2$ and the electron-rich ligand PCy_3 and $K_2HPO_4{\cdot}3H_2O$ or an aqueous solution of $NaHCO_3$ as the base under experimental conditions (Table 2, entries 6 and 7) similar to those reported by Wu, Zhang et al.[23] for the Suzuki-type reaction of 3-aryl- or 3-bromo-4-(tosyloxy)coumarins with arylboronic acids, respectively. Good results were obtained in particular when the reaction was carried out using an aqueous solution of $NaHCO_3$ as base. Under these experimental

Table 2. Optimization of the reaction conditions for the cross-coupling reaction between tosylate **3a** and phenylboronic acid (**4a**).



Entry	Transition metal compound (%)	Ligand [mol-%]	Base [equiv.]	Solvent	Reaction conditions [°C/h]	Yield (%)[a]
1	$RhCl(PPh_3)_3$ (2.0)	dppf (2.0)	CsF (4.0)	toluene/H_2O (1:1)	50/28	–
2[b]	$PdCl_2(PPh_3)_2$ (5.0)	–	CsF (3.0)	toluene/H_2O (1:1)	60/25	12
3[b]	$PdCl_2$(dppf) (5.0)	–	CsF (3.0)	toluene/H_2O (1:1)	110/28	23
4[b]	$PdCl_2(PhCN)_2$ (5.0)	XantPhos (5.0)	CsF (3.0)	toluene/H_2O (1:1)	110/22	53
5[b]	$PdCl_2(PhCN)_2$ (5.0)	(*S*)-BINAP (5.0)	CsF (3.0)	toluene/H_2O (1:1)	110/48	trace
6	$Pd(OAc)_2$ (5.0)	PCy_3 (10.0)	$K_2HPO_4{\cdot}3H_2O$ (3.0)	MeOH	60/1.5	29
7	$Pd(OAc)_2$ (5.0)	PCy_3 (10.0)	$NaHCO_3$ 1 M in H_2O (3.0)	MeOH	60/1.5	65
8	$Pd(OAc)_2$ (5.0)	PCy_3 (10.0)	K_2HPO_4 (3.0)	MeOH	60/1.5	52
9	$Pd(OAc)_2$ (5.0)	PCy_3 (10.0)	$NaHCO_3$ (3.0)	MeOH	60/1.5	90
10	$Pd(OAc)_2$ (5.0)	PPh_3 (10.0)	$NaHCO_3$ (3.0)	MeOH	60/1.5	trace
11	$Pd(OAc)_2$ (5.0)	dppf (5.0)	$NaHCO_3$ (3.0)	MeOH	60/1.5	trace

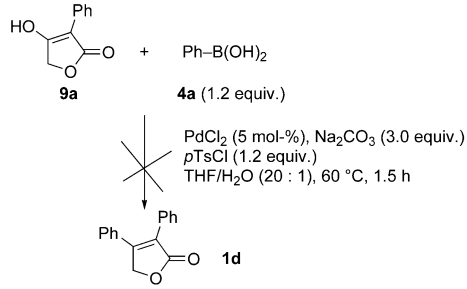
[a] Isolated yield based on tosylate **3a**. [b] Reaction performed in the presence of 5 mol-% $BnEt_3NCl$.

conditions compound **1d** was isolated in 65% yield (Table 2, entry 7).

We next found that, in contrast to what reported for the arylation of 3-aryl-4-tosyloxycoumarins and 3-bromo-4-(tosyloxy)coumarins,[23] the yield of **1d** was improved when the reaction between **3a** and **4a** was carried out in the presence of anhydrous inorganic bases. In fact, the use of anhydrous K_2HPO_4 instead of the corresponding hydrated salt caused an increase of the yield from 29 to 52% (compare entries 6 and 8 of Table 2). Moreover, a more remarkable improvement of the yield of **1d** was obtained when the $Pd(OAc)_2/PCy_3$-catalyzed reaction of **3a** with **4a** was carried out in methanol at 60 °C in the presence of solid $NaHCO_3$ as the base (Table 2, entry 9). Compound **1d** was cleanly obtained in 90% isolated yield. On the contrary, the use of ligands for palladium different from PCy_3, such as PPh_3 and dppf, gave unsatisfactory results (Table 2, entries 10 and 11).

The preparation of **1a** by reaction of 4-hydroxy-3-phenyl-2(5*H*)-furanone (**9a**) with 1.2 equiv. of **4a** in a 20:1 mixture of THF and water at 60 °C for 1.5 h in the presence of 1.1 equiv. of *p*-toluenesulfonyl chloride, 3.0 equiv. of Na_2CO_3 and 5 mol-% $PdCl_2$ (Scheme 2), according to a recently described protocol for the palladium-catalyzed direct arylation of 4-hydroxycoumarins,[24] was also attempted. Unfortunately, the reaction did not provide any trace of **1d** despite the absence of **9a** in the crude reaction mixture.

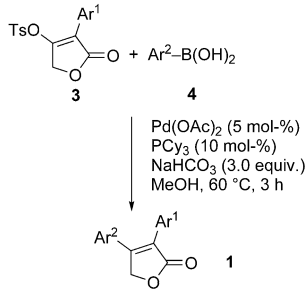
Nevertheless, encouraged by the results obtained in entry 11 of Table 2, we next investigated the scope of this cross-coupling reaction by using tosylates **3c** and **3b**, bearing aryl moieties substituted with one electron-withdrawing and three electron-donating groups, respectively, at their activated C-4 position and arylboronic acids **4b**–**e** as substrates under the experimental condition of this entry. The boronic acids were characterized by electron-neutral, electron-rich or electron-deficient aryl moieties. As shown in Table 3, the examined reactions (entries 1–5) generated the desired



Scheme 2. Attempted synthesis of **1d** by direct arylation of **9a**.

chemically pure unsymmetrical 3,4-diaryl-substituted 2(5*H*)-furanones **1b**, **1e**, **1f**, **1g**, and **1h** in 90, 54, 70, 83 and 76% yield, respectively.

Table 3. Coupling of activated tosylates **3b** and **3c** with arylboronic acids.



Entry	3	Ar^1	4	Ar^2	1	Yield (%)
1	**3b**	3,4,5-$(MeO)_3C_6H_2$	**4b**	2-naphthyl	**1b**	90
2	**3b**	3,4,5-$(MeO)_3C_6H_2$	**4c**	3-F,4-$MeOC_6H_3$	**1e**	54
3	**3b**	3,4,5-$(MeO)_3C_6H_2$	**4d**	4-AcC_6H_4	**1f**	70
4	**3c**	4-$CF_3C_6H_4$	**4e**	4-$MeOC_6H_4$	**1g**	83
5	**3c**	4-$CF_3C_6H_4$	**4b**	2-naphthyl	**1h**	76

Finally, we turned our attention to the application of the optimized reaction conditions used in entry 11 of Table 2 and entries 1–5 of Table 3 for the preparation of 4-aryl-6-methyl-2(2*H*)-pyranones **6** from 6-methyl-4-tosyloxy-2(2*H*)-pyranone (**5**) and arylboronic acids. Compound **5** was obtained in 70% yield from commercially available 4-hydroxy-6-methyl-2(2*H*)-pyranone (triacetic acid lactone) (**10**) (Figure 3) according to a literature procedure.[25]

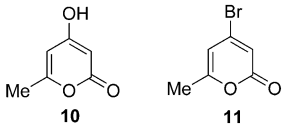
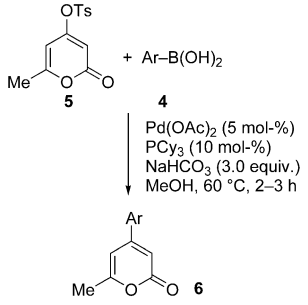


Figure 3. Chemical structures of compounds **10** and **11**.

As shown in Table 4, these palladium-catalyzed cross-coupling reactions enabled the synthesis of compounds **6a**–**d** in high yields (entries 1,4).

Table 4. Coupling of 6-methyl-4-tosyloxy-2(2*H*)-pyranone (**5**) with arylboronic acids.



Entry	4	Ar	Reaction time [h]	Product	Yield (%)
1	**4a**	Ph	3	**6a**	84
2	**4e**	4-$MeOC_6H_4$	2	**6b**	70
3	**4f**	4-$CF_3C_6H_4$	2	**6c**	96
4	**4d**	4-AcC_6H_4	2	**6d**	76

The results of this procedure for the synthesis of compounds **6** thus proved to compete favourably with those recently reported in the literature[15] in which these heterocycle derivatives were synthesized in modest to high yields via Suzuki-type reaction of arylboronic acids with 4-bromo-6-methyl-2(2*H*)-pyranone (**11**) (Figure 3), obtained in 78% yield by treatment of **10** with PBr_3 in a mixture of Et_2O and DMF. Moreover, in this literature procedure the highest yields were obtained when a mixture of $Pd(OAc)_2$ and 2-(di-*tert*-butylphosphanyl)biphenyl, a quite expensive bulky ligand, was used as the catalyst precursor.[15] It is also worth mentioning that yields of compounds **6** that are similar to those reported in Table 4, have been recently obtained by Suzuki-type cross-coupling of **5** with arylboronic acids in the presence of a catalytic amount of a *N*-heterocycle carbene-derived nickel-pincer complex.[19a] However, this complex is not commercially available and the cross-coupling reactions catalyzed by this complex occur at higher temperatures and with longer reaction times than those of our mild procedure.

Conclusions

Both symmetrical and unsymmetrical 3,4-diaryl-substituted 2(5*H*)-furanones, including 4-(2-naphthyl)-3-(3,4,5-trimethoxyphenyl)-2(5*H*)furanone (**1b**), which was shown to be highly cytotoxic against the NCI human tumor cell lines panel,[10h] have been prepared in high yields via an inexpensive procedure involving an unprecedented $Pd(OAc)_2$/PCy_3-catalyzed Suzuki-type cross-coupling reaction of arylboronic acids containing electron-rich, electron-neutral and electron-deficient aryl moieties with readily available 3-aryl-4-tosyloxy-2(5*H*)-furanones as the key step. The mild experimental reaction conditions of this procedure, in which methanol is used as the solvent and $NaHCO_3$ is employed as the base, have also proven to be suitable for the high yielding synthesis of 4-aryl-6-methyl-2(2*H*)-pyranones from 6-methyl-4-tosyloxy-2(2*H*)-pyranone. Investigations in which the mild $Pd(OAc)_2$/PCy_3-catalyzed arylation procedure developed in this study is applied are in progress. The focus is on large-scale syntheses of new unsymmetrical 3,4-diaryl-substituted 2(5*H*)-furanones that are suitable for in vivo tests, more water-soluble, and possess higher cytotoxicity against human tumor cell lines than the furanone derivatives tested so far.

Experimental Section

General Procedure for the Suzuki-Type Reaction between 3-Aryl-4-tosyloxy-2(5*H*)-furanones 3 and Arylboronic Acids 4: A 3-aryl-4-tosyloxy-2(5*H*)-furanone **3** (1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PCy_3 (28.0 mg, 0.1 mmol), $NaHCO_3$ (252 mg, 3.0 mmol), and an arylboronic acid **4** (1.5 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 methanol (16 mL) was added by syringe and the mixture was stirred under argon at 60 °C for 3 h. After this period of time, the reaction – monitored by GLC and TLC analyses of a sample of the crude reaction mixture after it had been diluted with AcOEt and filtered through Celite® – was complete. The reaction mixture was then allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with AcOEt (25 mL), poured into water (100 mL) and the resulting mixture was extracted with AcOEt (4 × 25 mL). The combined organic extracts were washed with brine, dried and concentrated under reduced pressure. The resulting solid residue was purified by MPLC or flash chromatography on silica gel or by recrystallization. This procedure was employed to prepare 3,4-diaryl-2(5*H*)-furanones **1b** and **1d**–**h**.

4-(2-Naphthyl)-3-(3,4,5-trimethoxyphenyl)-2(5*H*)-furanone (1b): The crude product obtained from the Suzuki-type reaction between 3-(3,4,5-trimethoxyphenyl)-4-tosyloxy-2(5*H*)-furanone (**3b**) and 2-naphthylboronic acid (**4b**) (Table 3, entry 1) was purified by recrystallization from a mixture of CH_2Cl_2 and petroleum ether to give **1b** (341 mg, 90%) as a colourless solid, m.p. 206 °C (ref.[10g] m.p. 199–202 °C). EI–MS: *m*/*z* (%) = 377 (26) [M^+ + 1], 376 (100) [M^+], 361 (11), 202 (11), 189 (10). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (m, 4 H), 7.55 (m, 2 H), 7.40 (m, 1 H), 6.73 (s, 2 H), 5.30 (s, 2 H), 3.89 (s, 3 H), 3.70 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.5, 155.7, 153.2 (2 C), 148.8, 134.0 (2 C), 133.1 (2 C), 128.6, 128.3, 127.9, 127.4, 127.1, 126.0, 125.5, 124.7, 106.6 (2

C), 70.6, 61.0, 56.1 (2 C) ppm. The spectroscopic data for this 99% chemically pure compound were in agreement with those previously reported.[10g]

4-(3-Fluoro-4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2(5*H*)-furanone (1e): The crude product obtained from the Suzuki-type reaction between 3-(3,4,5-trimethoxyphenyl)-4-tosyloxy-2(5*H*)-furanone (**3b**) and (3-fluoro-4-methoxyphenyl)boronic acid (**4c**) (Table 3, entry 2) was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and AcOEt (93:7) as eluent, to give **1e** (201 mg, 54%) as a pale orange solid, m.p. 124 °C. EI–MS: *m*/*z* (%) = 375 (23) [M^+ + 1], 374 (100) [M^+], 359 (15), 331 (11), 317 (11). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.13 (m, 2 H), 6.94 (m, 1 H), 6.65 (s, 2 H), 5.14 (s, 2 H), 3.90 (d, J = 5.4 Hz, 6 H), 3.80 (m, 6 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 173.4, 154.0, 153.6 (2 C), 149.8, 149.7, 138.8, 125.4, 125.3, 124.4, 124.3, 115.5, 115.1, 113.4, 106.5 (2 C), 70.2, 56.3, 56.2 (2 C) ppm. GLC analysis showed that **1e** had chemical purity higher than 99%. $C_{20}H_{19}FO_6$ (374.36): calcd. C 64.17, H 5.12; found C 64.09, H 5.07.

4-(4-Methoxyphenyl)-3[4-(trifluoromethyl)phenyl]-2(5*H*)-furanone (1g): The crude product obtained from the Suzuki-type reaction between 3-[4-(trifluoromethyl)phenyl]-4-tosyloxy-2(5*H*)-furanone (**3c**) and (4-methoxyphenyl)boronic acid (**4e**) (Table 3, entry 4) was purified by recrystallization from a mixture of CH_2Cl_2 and petroleum ether to give **1g** (276 mg, 83%) as a pale yellow solid, m.p. 148 °C. EI–MS: *m*/*z* (%) = 335 (20) [M^+ + 1], 334 (100) [M^+], 305 (18), 277 (78), 262 (17). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (m, 2 H), 7.57 (m, 2 H), 7.26 (m, 2 H), 6.87 (m, 2 H), 5.19 (s, 2 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.2, 161.9, 157.4, 134.5, 131.0, 130.3, 129.8 (2 C), 129.2 (2 C), 125.7 (2 C), 123.0, 122.5, 114.7 (2 C), 70.6, 55.4 ppm. GLC analysis showed that **1g** had chemical purity higher than 98.5%. $C_{18}H_{13}F_3O_3$ (334.29): calcd. C 64.67, H 3.92; found C 64.54, H 3.85.

General Procedure for the Suzuki-Type Reaction between 6-Methyl-4-tosyloxy-2(2*H*)-pyranone (5) and Arylboronic Acids: Compound **5** (280 mg, 1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PCy_3 (28 mg, 0.1 mmol), $NaHCO_3$ (252 mg, 3.0 mmol), and an arylboronic acid **4** (1.5 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 methanol (10 mL) was added by syringe and the mixture was stirred under argon at 60 °C for the period of time reported in Table 4. After this period the reaction was complete. The reaction mixture was then allowed to cool to room temperature, filtered through Celite®, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. Compounds **6a**–**d** were prepared according to this general procedure.

6-Methyl-4-[4-(trifluoromethoxy)phenyl]-2(2*H*)-pyranone (6c): The crude product obtained from the Suzuki-type reaction between **5** and [4-(trifluoromethoxy)phenyl]boronic acid (**4f**) (Table 4, entry 3) was purified by MPLC on silica gel, with a mixture of toluene and AcOEt (85:15) as eluent, to give **6c** (259 mg, 96%) as a pale yellow solid, m.p. 62 °C. EI–MS: *m*/*z* (%) = 270 (33) [M^+], 243 (13), 242 (100), 199 (38), 69 (10). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.61 (m, 2 H), 7.32 (m, 2 H), 6.33 (s, 1 H), 6.27 (s, 1 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 163.1, 162.7, 154.1, 150.9, 134.5, 128.4 (2 C), 123.0, 121.4 (2 C), 108.6, 103.2, 20.2 ppm. GLC analysis showed that **6c** had chemical purity higher than 99%. $C_{13}H_9F_3O_3$ (270.20): calcd. C 57.79, H 3.36; found C 57.63, H 3.31.

4-(4-Acetylphenyl)-6-methyl-2(2*H*)-pyranone (6d): The crude product obtained from the Suzuki-type reaction between **5** and (4-acetylphenyl)boronic acid (**4d**) (Table 4, entry 4) was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and AcOEt (90:10) as eluent, to give **6d** (174 mg, 76%) as a pale yellow solid, m.p. 175 °C. EI–MS: *m*/*z* (%) = 228 (34) [M^+], 200 (26), 185 (100), 157 (10), 128 (13). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.06 (m, 2 H), 7.67 (m, 2 H), 6.38 (s, 1 H), 6.33 (s, 1 H), 2.65 (s, 3 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 197.1, 162.9, 162.7, 154.3, 140.2, 138.5, 129.1 (2 C), 127.0 (2 C), 109.3, 103.2, 26.7, 20.2 ppm. GLC analysis showed that **6c** had chemical purity higher than 98.7%. $C_{14}H_{12}O_3$ (228.24): calcd. C 73.67, H 5.30; found C 73.63, H 5.21.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and characterization for compounds **1d**, **1f**, **1h**, **3a**–**c**, **5**, **6a**, **6b**, **and 9a**–**c**.

[1] For reviews on this topic, see: a) N.-H. Nam, *Curr. Med. Chem.* **2003**, *10*, 1697–1722; b) F. Bellina, R. Rossi, *Tetrahedron* **2006**, *62*, 7213–7256; c) G. C. Tron, T. Pirali, G. Sorba, F. Pagliai, S. Busacca, A. A. Genazzani, *J. Med. Chem.* **2006**, *49*, 3033–3044; d) F. Bellina, S. Cauteruccio, R. Rossi, *Tetrahedron* **2007**, *63*, 4571–4624.

[2] a) Y. Leblanc, J. Y. Gautthier, D. Ethier, J. Guay, J. A. Mancini, D. Riendeau, P. Tagari, P. J. Vickers, E. Wong, P. Prasit, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2123–2128; b) J. J. Talley, *Prog. Med. Chem.* **1999**, *36*, 201–234; c) A. Zarghi, P. N. Praven Rao, E. E. Knaus, *J. Pharm. Pharmaceut. Sci.* **2007**, *10*, 159–167.

[3] G.-B. Liang, X. Qian, D. Feng, M. Fisher, T. Crumley, S. J. Darkin-Rattray, P. M. Dulski, A. Gurnett, P. S. Leavitt, P. A. Liberator, A. S. Misura, S. Samaras, T. Tamas, D. M. Schmatz, M. Wyvratt, T. Biftu, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2019–2022.

[4] J. Y. Kim, H. J. Seo, S.-H. Lee, M. E. Jung, K. Ahn, J. Kim, J. Lee, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 142–145.

[5] J. A. Pfefferkorn, S. D. Larsen, C. Van Huis, R. Sorenson, T. Barton, T. Winters, B. Auerbach, C. Wu, T. J. Wolfram, H. Cai, K. Welch, N. Esmaiel, J. Davis, R. Bousley, K. Olsen, S. B. Mueller, T. Mertz, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 546–553.

[6] L. Gomez, M. D. Hack, K. McClure, C. Sehon, L. Huang, M. Morton, L. Li, T. D. Barrett, N. Shankley, J. G. Breitenbucher, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6493–6498.

[7] a) D. Bonafoux, C. Chaqui, P. A. Boriack-Sjodin, C. Fitch, G. Hankins, S. Josiah, C. Black, G. Hetu, L. Ling, W.-C. Lee, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 912–916; b) D.-K. Kim, J. H. Choi, Y. J. An, H. S. Lee, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2122–2127.

[8] a) M. Mader, A. de Dios, C. Shih, R. Bonjouklian, T. Li, W. White, B. L. Uralde, C. Sánchez-Martinez, M. del Prado, C. Jaramilla, E. de Diego, L. M. M. Cabrejas, C. Dominguez, C. Montero, T. Sheperd, R. Dally, J. E. Toth, A. Chatterjee, S. Plette, J. Blanco-Urgoiti, L. Perez, M. Barberis, M. J. Lorite, E. Jambrina, C. R. Nevill Jr., P. A. Lee, R. C. Schultz, J. A. Wolos, L. C. Li, R. M. Campbell, B. D. Anderson, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 179–183; b) P. Dinér, T. Andersson, J. Kjelén, K. Elbing, S. Hohmann, M. GrØtli, *New J. Chem.* **2009**, *33*, 1010–1016.

[9] W. K. C. Park, R. M. Kennedy, S. D. Larsen, S. Miller, B. D. Roth, Y. Song, B. A. Steinbaugh, K. Sun, B. D. Tait, M. C. Kowala, B. K. Trivedi, B. Auerbach, V. Askew, L. Dillon, J. C. Hanselman, Z. Lin, G. H. Lu, A. Robwertson, C. Seberke, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1151–1156.

[10] a) F. Bellina, S. Cauteruccio, A. Di Fiore, R. Rossi, *Eur. J. Org. Chem.* **2008**, 5436–5445; b) K. Odlo, J. Hentzen, J. Fournier dit Chabert, S. Ducki, O. A. B. S. M. Gani, I. Sylte, M. Skrede, V. A. Florens, T. V. Hansen, *Bioorg. Med. Chem.* **2008**, *16*, 4829–4838; c) M. Wu, Q. Sun, C. Yang, D. Chen, J. Ding, Y. Chen, L. Lin, Y. Xie, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 869–873; d) F. Bellina, S. Cauteruccio, S. Monti, R. Rossi, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3153–3158; e) J. Kaffy, R. Pontikis, D. Carrez, A. Croisy, C. Monneret, J.-C. Florent, *Bioorg. Med. Chem.* **2006**, *14*, 4067–4077; f) L. Sun, N. I. Vasilev-

ich, J. A. Fuselier, D. H. Coy, *Anticancer Res.* **2004**, *24*, 179–186; g) F. Bellina, C. Anselmi, F. Martina, R. Rossi, *Eur. J. Org. Chem.* **2003**, 2290–2302; h) F. Bellina, R. Rossi, *26th Winter Meeting of the EORTC–PAMM Group*, January 26–29, **2005**, Arcachon, France, *Abstracts* P9; i) L. Wang, K. W. Woods, Q. Li, K. J. Barr, R. W. McCroskey, S. M. Hannick, L. Gherke, R. B. Credo, Y.-H. Hui, K. Marsh, R. Warner, J. Y. Lee, N. Zielinski-Mozng, D. Frost, S. H. Rosenberg, H. L. Sham, *J. Med. Chem.* **2002**, *45*, 1697–1711; j) Y. Kim, N.-H. Nam, Y.-J. You, B.-Z. Ahn, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 719–722; k) N.-H. Nam, Y. Kim, Y.-J. You, D.-H. Hong, H.-M. Kim, B.-Z. Ahn, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3073–3076; l) K. Ohsumi, T. Hatanaka, K. Fujita, R. Nakagawa, Y. Fukuda, Y. Nihei, Y. Suga, Y. Morinaga, Y. Akiyama, T. Tsuji, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3153–3158.

[11] a) L. A. Sorbera, X. Rabasseda, J. Castaner, *Drugs Fut.* **1998**, *23*, 1287; b) C. C. Chan, S. Boyce, C. Brideau, S. Charleson, W. Cromlish, D. Ethier, J. Evans, A. W. Ford-Hutchinson, M. J. Forrest, J. Y. Gauthier, R. Gordon, M. Gresser, J. Guay, S. Kargman, B. Kennedy, Y. Leblanc, S. Leger, J. Mancini, G. . O'Neill, M. Ouellet, D. Patrick, M. D. Percival, H. Perrier, P. Prasit, I. Rodger, P. Tagari, M. Therien, P. Vickers, D. Visco, W. Wang, J. Webb, E. Wong, L.-J. Xu, R. N. Young, R. Zamboni, D. Riendeau, *J. Pharmacol. Exp. Ther.* **1999**, *290*, 551–560.

[12] R. S. Breselier, R. S. Sandler, H. Quan, J. A. Bolognese, B. Oxenius, K. Horgan, C. Lines, R. Riddel, D. Morton, A. Lanas, M. A. Konstam, J. A. Baron, *N. Engl. J. Med.* **2005**, *352*, 1092–1102.

[13] G. R. Pettit, S. B. Singh, E. Hamel, C. M. Lin, D. S. Alberts, D. Garcia-Kendall, *Experientia* **1989**, *45*, 209–211.

[14] a) F. Toda, Y. Takehira, Y. Kataoka, K. Mori, T. Sato, M. Segawa, *J. Chem. Soc., Chem. Commun.* **1984**, 1234–1235; b) S. T. Vijaraghavan, T. R. Balasubramanian, *Indian J. Chem. Sect. B* **1986**, *25*, 760–761; c) R. Mahon, A. M. E. Richecoeur, J. B. Sweeney, *J. Org. Chem.* **1999**, *64*, 328–329; d) P. Forgione, P. D. Wilson, A. G. Fallis, *Tetrahedron Lett.* **2000**, *41*, 17–20; e) R. Rossi, F. Bellina, E. Raugei, *Synlett* **2000**, 1749–1751; f) J. Zhang, P. G. Blazecka, D. Belmont, J. G. Davidson, *Org. Lett.* **2002**, *4*, 4559–4561.

[15] I. J. S. Fairlamb, L. R. Marrison, J. M. Dickinson, F.-J. Lu, J. P. Schmidt, *Bioorg. Med. Chem.* **2004**, *12*, 4285–4299.

[16] A. Mallinger, T. Le Gall, C. Mioskowski, *J. Org. Chem.* **2009**, *74*, 1124–1129.

[17] For papers on rhodium-catalyzed cross-coupling reactions of activated alkenyl tosylates with arylboronic acids, see: a) J. Wu, L. Zhang, Y. Luo, *Tetrahedron Lett.* **2006**, *47*, 6747–6750; b) J. Wu, L. Zhang, K. Gao, *Eur. J. Org. Chem.* **2006**, 5260–5263.

[18] For papers on palladium-catalyzed cross-coupling reactions of alkenyl tosylates with organoboron compounds, see: a) T. M. Gøgsig, L. S. Søberg, A. T. Lindhardt, K. L. Jensen, T. Skrydstrup, *J. Org. Chem.* **2008**, *73*, 3404–3410; b) H. Nakatsuji, K. Ueno, T. Misaki, Y. Tanabe, *Org. Lett.* **2005**, *7*,2131–2134; c) D. Steinhuebel, J. M. Baxter, M. Palucki, I. W. Davies, *J. Org. Chem.* **2005**, *70*, 10124–10127; d) J. M. Baxter, D. Steinhuebel, M. Palucki, I. W. Davies, *Org. Lett.* **2005**, *7*, 215–218; e) J. Wu, Q. Zhu, L. Wang, R. Fathi, Z. Yang, *J. Org. Chem.* **2003**, *68*, 670–673; f) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.

[19] For papers on nickel-catalyzed cross-coupling reactions of alkenyl tosylates with arylboronic acids, see: a) J.-i. Kuroda, K. Inamoto, K. Hiroya, T. Doi, *Eur. J. Org. Chem.* **2009**, 2251–2261; b) Z.-Y. Tang, Q.-S. Hu, *Adv. Synth. Catal.* **2004**, *346*, 1635–1637.

[20] E. Alacid, C. Nájera, *Org. Lett.* **2008**, *10*, 5011–5014.

[21] a) G. A. Molander, B. Biolatto, *Org. Lett.* **2002**, *4*, 1867–1870; b) M. Pucheault, S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2002**, 3552–3557; c) G. A. Molander, T. Ito, *Org. Lett.* **2001**, *3*, 393–396; d) R. A. Batey, T. D. Quach, *Tetrahedron Lett.* **2001**, *42*, 9099–9103.

[22] P. W. N. W. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741–2769.

[23] L. Zhang, T. Meng, R. Fan, J. Wu, *J. Org. Chem.* **2007**, *72*, 7279–7286.

[24] Y. Luo, J. Wu, *Tetrahedron Lett.* **2009**, *50*, 2103–2105.

[25] A. M. Bittencourt, O. R. Gottlieb, W. B. Mors, M. T. Magalhães, S. Mageswaran, W. D. Ollis, I. O. Sutherland, *Tetrahedron* **1971**, *27*, 1043–1048.

Received: May 26, 2009
Published Online: August 6, 2009

