DOI: 10.1002/adsc.200700038

Palladium-Catalyzed Regioselective Cross-Coupling Reactions of 3-Bromo-4-tosyloxyquinolin-2(1*H*)-one with Arylboronic Acids. A Facile and Convenient Route to 3,4-Disubstituted Quinolin-2(1*H*)-ones

Zhiyong Wang,[a] Renhua Fan,[a] and Jie Wu[a,b,*]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, People's Republic of China
Fax: (+86)-216-510-2412; e-mail: jie_wu@fudan.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, People's Republic of China

Received: January 22, 2007

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The palladium-catalyzed regioselective cross-coupling reaction of 3-bromo-4-tosyloxyquinolin-2(1*H*)-one with arylboronic acid is described, which provides a simple, general, efficient, and practical route for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones.

Keywords: arylboronic acids; cross-coupling; homogeneous catalysis; palladium; quinolin-2(1*H*)-ones; regioselectivity

Introduction

High-throughput screening has created a critical demand to develop practical routes for the rapid chemical synthesis of natural product-like molecules. To secure such practice, the discovery and invention of new synthetic methods for accessing some natural product entities in more efficient ways has been a fertile area of organic synthesis.[1] Although numerous synthetic methods exists in the literature which allow the chemists to synthesize the intriguing molecules individually, nevertheless, it is highly desirable to develop even more effective synthetic methodologies for heterocycle formation in order to build up complex natural product-like molecules in a combinatorial format.

As a privileged fragment, the quinolin-2(1*H*)-one core is a ubiquitous subunit in many alkaloids with remarkable biological activities. Members of this family have wide applications in medicinal chemistry, being used as anticancer,[2] antiviral,[3] and antihypertensive agents.[3] Moreover, quinolin-2(1*H*)-ones are also valuable intermediates in organic synthesis, since they are easily converted into 2-chloro- and then 2-aminoquinoline derivatives.[4] As part of a continuing effort in our laboratory toward the development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds,[5] we became interested in the possibility of developing efficient methods for the synthesis of diversified quinolin-2(1*H*)-one molecules which include four centers for the introduction of diversity into the quinolin-2(1*H*)-one molecule (Figure 1). Herein, we describe our recent efforts for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones *via* palladium-catalyzed regioselective cross-coupling reactions[6] of 3-bromo-4-tosyloxyquinolin-2(1*H*)-one with arylboronic acids.

Although there are classic methods for the generation of a broad range of 3- or 4-substituted quinolin-2(1*H*)-ones,[7–9] the utility of these reactions for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones is quite limited.[10] On the other hand, several other methods including palladium-catalyzed reactions for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones are usually complicated by low yields, harsh condi-

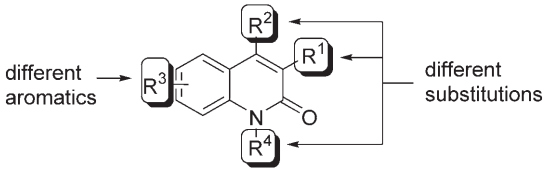
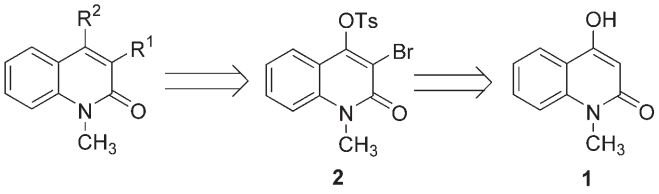


Figure 1.



Scheme 1.

tions, and limitations of substrate scope.[11–17] Thus, it is of great interest to develop general protocols for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones under mild reaction conditions.

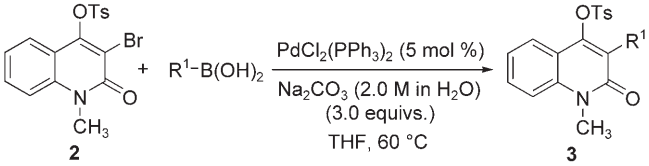
Prompted by the recent advances in the halogenation of 1,3-dicarbonyl compounds,[18] we envisioned that 3-bromo-4-hydroxyquinolin-2(1*H*)-one could be generated from commercially available 4-hydroxyquinolin-2(1*H*)-one **1**. This compound could be further elaborated to afford 3-bromo-4-tosyloxyquinolin-2(1*H*)-one **2** after reaction with *p*-toluenesulfonyl chloride in the presence of triethylamine (Scheme 1). On the other hand, recently we found that the 4-tosyloxy group attached to the electron-withdrawing α,β-unsaturated double bond increased its capability for oxidative addition to transition metals[5] although arenesulfonates are relatively unreactive compared to the corresponding halides and triflates.[19] Based on the results in which oxidative addition of the C(sp^2)–Br bond to the transition metal is easier than that of the C(sp^2)–OTs bond in cross-coupling reactions, we conceived that the regioselective cross-coupling of 3-bromo-4-tosyloxyquinolin-2(1*H*)-one may be fulfilled under suitable conditions. Due to their easy handling and long shelf life, arylboronic acid derivatives would be the starting materials of choice. Thus, we started to explore the possibility of regioselective Suzuki–Miyaura coupling reaction[20] by using 3-bromo-4-tosyloxyquinolin-2(1*H*)-one **2** as an electrophile for the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones.

Results and Discussion

Our studies commenced with the reaction of 3-bromo-4-tosyloxyquinolin-2(1*H*)-one **2** with phenylboronic acid catalyzed by $PdCl_2(PPh_3)_2$ (5 mol%) in THF at room temperature. (Scheme 2) To our delight, as expected we observed the formation of the desired product **3a** and 50% of isolated yield was obtained after 12 h as well as recovery of the starting material. The result was dramatically improved when the reaction was performed at 60 °C (95% yield, 12 h). In this reaction, only the 3-position was substituted and the 4-tosyloxy group was retained even in the presence of 3.0 equivs. of phenylboronic acid.

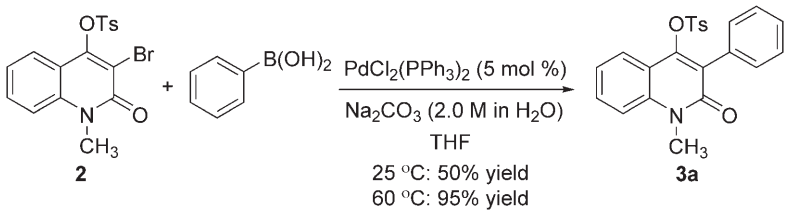
With this promising result in hand, we started to investigate the cross-coupling reactions between 3-bromo-4-tosyloxyquinolin-2(1*H*)-one **2** and various arylboronic acids without optimization of the reaction conditions, and the results are shown in Table 1. From Table 1, we found that this conditions allowed us to perform a broad range of cross-coupling reactions within 12 h. Thus, 2- or 4-methoxyphenylboronic acid reacted with substrate **2** in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) and sodium carbonate (2.0 M in water, 3.0 equivs.) in THF at 60 °C to give the cross-coupling product **3b** or **3c** in 90% or 98% yield, respectively (entries 2 and 3, Table 1). Similarly, the reaction of **2** with 4-methylphenylboronic acid furnished the expected product **3d** in 96% yield (entry 4).

Table 1. Cross-coupling reactions between 3-bromo-4-tosyloxyquinolin-2(1*H*)-one **2** and arylboronic acids.



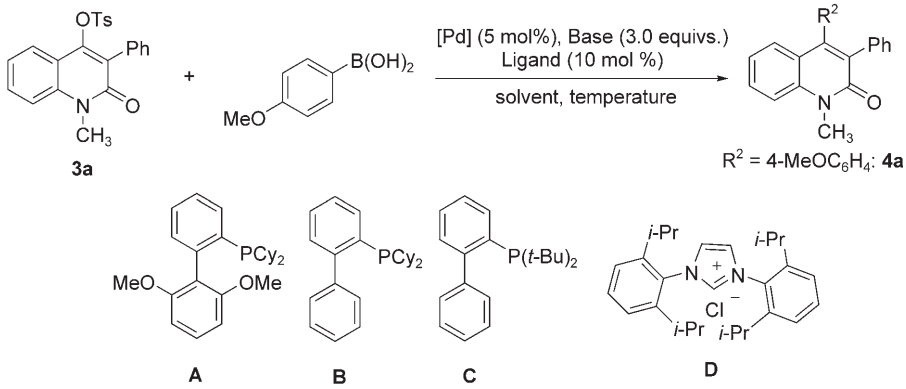
Entry	R^1	Product	Yield [%][a]
1	C_6H_5	**3a**	95
2	2-$MeOC_6H_4$	**3b**	90
3	4-$MeOC_6H_4$	**3c**	98
4	4-MeC_6H_4	**3d**	96
5	4-$CF_3C_6H_4$	**3e**	88
6	3-$CF_3C_6H_4$	**3f**	95
7	4-NCC_6H_4	**3g**	62
8	3-NCC_6H_4	**3h**	55
9	4-AcC_6H_4	**3i**	90

[a] Isolated yield based on 3-bromo-4-tosyloxyquinolin-2(1*H*)-one **2**.



Scheme 2.

Table 2. Reaction of compound **3a** with 4-methoxyphenylboronic acid under various conditions.



Entry	[Pd]	L	Base	Solvent	*T* [°C]	Yield [%][a]
1	$PdCl_2(PPh_3)_2$	-	KF	THF	60	n.r.
2	$Pd(PPh_3)_4$	-	KF	THF	60	n.r.
3	$Pd(PPh_3)_4$	-	KF	dioxane	100	n.r.
4	$PdCl_2(PPh_3)_2$	-	KF	toluene	110	n.r.
5	$PdCl_2(PPh_3)_2$	-	Na_2CO_3	toluene	110	n.r.
6	$Pd(OAc)_2$	**A**	K_3PO_4	THF	60	50
7	$Pd(OAc)_2$	**A**	K_3PO_4	*t*-BuOH	80	84
8	$Pd(OAc)_2$	**B**	K_3PO_4	*t*-BuOH	80	trace
9	$Pd(OAc)_2$	**C**	K_3PO_4	*t*-BuOH	80	n.r.
10	$Pd(OAc)_2$	PCy_3	K_3PO_4	*t*-BuOH	80	trace
11	$Pd(OAc)_2$	dppp	K_3PO_4	*t*-BuOH	80	trace
12	$Pd(OAc)_2$	dppf	K_3PO_4	*t*-BuOH	80	trace
13	$Pd(OAc)_2$	**D**	*t*-BuOK	*t*-BuOH	80	15

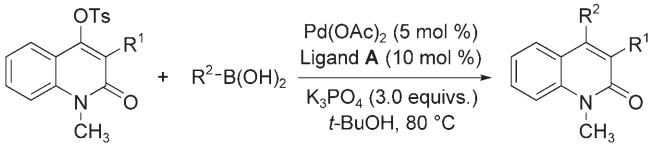
[a] Isolated yield based on substrate **3a**.

Cross-coupling of 3- or 4-trifluoromethylphenylboronic acid with **2** provided the desired products in 95% or 88% yield (entries 5 and 6). Arylboronic acids bearing a ketone function are compatible with the mild cross-coupling conditions, and 4-acetylphenylboronic acid reacted smoothly with **2** leading to the ketone **3i** in 90% yield (entry 9). 3- or 4-cyanophenylboronic acid reacted with **2** within 12 h affording the expected product in moderate yield (entries 7 and 8).

After introducing diversity in 3-position, we considered the further elaboration of compound **3** for realization the cross-coupling of 4-position. Substrates **3a** and 4-methoxyphenylboronic acid were selected for the model studies. As mentioned above, no reaction occurred under the conditions shown in Table 1. Screening the palladium catalyst, base, solvent, and temperature also gave disappointing results. (Table 2, entries 1–5) We next screened this reaction with various ligands such as phosphines, diphosphines, and N-heterocyclic carbenes (Table 2, entries 6–13). Gratifyingly, expected product **4a** (50% yield) was generated when the reaction was performed in the presence of palladium acetate (5 mol%), ligand **A**, and K_3PO_4 in THF at 60°C (entry 6). Changing the solvent to *tert*-butyl alcohol and increasing the temperature to 80°C improved the result (84% yield, entry 7). However, reduced reactivity and inferior results were displayed when other ligands were employed in the reaction (Table 2, entries 8–13). For example, only a 15% yield of **4a** was obtained when the precusor **D** of a N-heterocyclic carbene was utilized as ligand.

To demonstrate the generality of this method, we next investigated the scope of this reaction under the optimized conditions [*t*-BuOH, 5 mol% of $Pd(OAc)_2$, 10 mol% of Ligand A, K_3PO_4, 80°C) and the results are summarized in Table 3. As shown in Table 3, this method is equally effective for both substrate **3** and arylboronic acids. 3,4-Disubstituted quinolin-2(1*H*)-ones **4** were generated successfully in good yields. When 3-phenyl-4-tosyloxyquinolin-2(1*H*)-one **3a** was employed as substrate, a better result was generated for arylboronic acids attached to electron-donating groups. For examples, reaction of compound **3a** with 4-methoxyphenylboronic acid afforded the desired product **4a** in 84% yield (Table 3, entry 1), while 70% yield of **4c** was obtained when 3-trifluoromethylphenylboronic acid was used as the partner (Table 3, entry 3). For substrate **3** with different elec-

Table 3. Synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones.



Entry	R^1	R^2	Product	Yield [%][a]
1	C_6H_5 (**3a**)	4-$MeOC_6H_4$	**4a**	84
2	C_6H_5 (**3a**)	C_6H_5	**4b**	75
3	C_6H_5 (**3a**)	4-$CF_3C_6H_4$	**4c**	70
4	C_6H_5 (**3a**)	3-$CF_3C_6H_4$	**4d**	73
5	4-$MeOC_6H_4$ (**3c**)	3-$CF_3C_6H_4$	**4e**	68
6	3-$CF_3C_6H_4$ (**3f**)	3-$CF_3C_6H_4$	**4f**	70

[a] Isolated yield based on substrate **3**.

tronic demands on aromatic rings involving electron-donating and electron-withdrawing groups, similar results were obatined when reacted with trifluoromethyl-phenylboronic acid (Table 3, entries 5 and 6).

Meanwhile, disubstitution of 3-bromo-4-tosyloxyquinolin-2(1*H*)-one **2** with 3.0 equivs. of arylboronic acid was tested under the conditions shown in Table 3. Fortunately, this reaction also performed smoothly to afford the final product in good yield. For instance, reaction of 3-bromo-4-tosyloxyquinolin-2(1*H*)-one **2** with 4-methoxyphenylboronic acid furnished the desired disubstituted product **5a** in 88% yield (Scheme 3).

Conclusions

In summary, the palladium-catalyzed regioselective cross-coupling reactions of 3-bromo-4-tosyloxyquinolin-2(1*H*)-one with arylboronic acids disclosed herein represent a simple, general, efficient, and practical synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones. The advantages of this method include good substrate generality, mild reaction conditions, and experimental ease.

Experimental Section

General Procedure for the Cross-Coupling Reaction between 3-Bromo-4-tosyloxyquinolin-2(1*H*)-one 2 and Arylboronic Acids

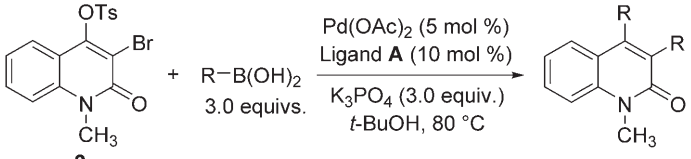
To a mixture of 3-bromo-4-tosyloxy-quinolin-2(1*H*)-one **2** (81.4 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), and boronic acid (1.5 equivs.) in THF (2 mL) was added potassium carbonate (2.0 M in water, 0.3 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 60 °C overnight. Following completion of the reaction as monitored by TLC, the reaction mixture was diluted with ethyl acetate (20 mL) and separated. The solution was dried and filtered, and the filtrate was concentrated to a residue which was purified by flash chromatography [silica gel, 2/1 (v/v) hexane/ethyl acetate] to give the corresponding product **3**.

1-Methyl-2-oxo-3-phenyl-1,2-dihydroquinolin-4-yl 4-methylbenzenesulfonate (3a):[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.25–7.16 (m, 8H), 7.03 (d, *J* = 7.8 Hz, 1H), 3.77 (s, 3H), 2.39 (s, 3H).

3-(2-Methoxyphenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl 4-methylbenzenesulfonate (3b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = (ppm) 8.12 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.28–7.12 (m, 5H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.85 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 157.1, 151.3, 144.6, 139.3, 133.4, 132.0, 131.3, 129.5, 129.3, 127.5, 125.4, 122.9, 122.3, 121.2, 120.1, 117.6, 113.9, 111.0, 55.5, 30.2, 21.6; MS: *m/z* (M^++1) = 436, calcd.: 436; HR-MS: *m/z* = 435.1145, calcd. for $C_{24}H_{21}NO_5S$:

3-(4-Methoxyphenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl 4-methylbenzenesulfonate (3c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 159.3, 150.5, 144.6, 138.8, 133.4, 132.0, 131.2, 129.3, 127.6, 125.3, 124.8, 123.7, 122.5, 117.9, 113.8, 113.1, 55.0, 30.2, 21.5; MS: *m/z* (M^++1) = 436, calcd. 436; HR-MS: *m/z* = 435.1143, calcd. for $C_{24}H_{21}NO_5S$: 435.1140.

1-Methyl-2-oxo-3-*p*-tolyl-1,2-dihydroquinolin-4-yl 4-methylbenzenesulfonate (3d): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.3 Hz, 1H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.26–7.24 (m, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 7.8 Hz, 2H), 3.75 (s, 3H), 2.40 (s, 3H), 2.31 (s, 3H);



5a: R = 4-$MeOC_6H_4$, 88% yield.
4f: R = 3-$CF_3C_6H_4$, 79% yield.
5b: R = 3-NCC_6H_4, 61% yield.

Scheme 3.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 150.6, 144.6, 138.9, 137.7, 133.3, 131.3, 120.5, 129.2, 128.6, 128.3, 127.6, 125.4, 125.2, 122.5, 117.8, 113.8, 30.2, 21.6, 21.3; MS: *m/z* (M^+ + 1) = 420, calcd.: 420; HR-MS: *m/z* = 419.1195, calcd. for $C_{24}H_{21}NO_4S$: 419.1191.

1-Methyl-2-oxo-3-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinolin-4-yl 4-methylbenzenesulfonate (3e): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.3 Hz, 1H), 7.69 (t, *J* = 7.3 Hz, 1H), 7.46–7.24 (m, 9H), 7.03 (d, *J* = 8.3 Hz, 2H), 3.77 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 151.4, 145.4, 139.3, 135.5, 133.0, 132.0, 131.2, 129.5, 129.4, 127.4, 125.7, 124.4, 123.6, 122.8, 117.5, 114.0, 30.3, 21.4; MS: *m/z* (M^+ + 1) = 474, calcd.: 474; HR-MS: *m/z* = 473.0906, calcd. for $C_{24}H_{18}F_3NO_4S$: 473.0909.

1-Methyl-2-oxo-3-(3-(trifluoromethyl)phenyl)-1,2-dihydroquinolin-4-yl 4-methylbenzenesulfonate (3f): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.22–7.16 (m, 2H), 7.08–7.03 (m, 4H), 3.77 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 151.1, 148.5, 145.4, 139.2, 133.6, 132.9, 131.9, 129.5, 129.3, 128.8, 127.5, 125.8, 123.5, 123.4, 122.7, 121.6, 116.4, 114.0, 30.3, 21.5; MS: *m/z* (M^+ + 1) = 474, calcd.: 474; HR-MS: *m/z* = 473.0905, calcd. for $C_{24}H_{18}F_3NO_4S$: 473.0909.

3-(4-Cyanophenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl 4-methylbenzenesulfonate (3g): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.41–7.34 (m, 5H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 3.78 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 151.6, 145.8, 139.4, 136.8, 133.6, 132.3, 131.7, 131.1, 129.6, 127.5, 125.7, 123.2, 122.9, 118.5, 117.4, 114.1, 111.4, 30.3, 21.6; MS: *m/z* (M^+ + 1) = 431, calcd.: 431; HR-MS: *m/z* = 430.0982, calcd. for $C_{24}H_{18}N_2O_4S$: 430.0987.

3-(3-Cyanophenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl 4-methylbenzenesulfonate (3h): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.46–7.31 (m, 9H), 7.13 (d, *J* = 7.8 Hz, 1H), 3.77 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 151.4, 145.8, 139.3, 135.4, 134.3, 133.2, 133.0, 132.2, 131.1, 129.8, 128.3, 127.5, 125.8, 122.9, 122.7, 118.2, 117.3, 114.0, 112.0, 29.6, 21.6; MS: *m/z* (M^+ + 1) = 431, calcd.: 431; HR-MS: *m/z* = 430.0984, calcd. for $C_{24}H_{18}N_2O_4S$: 430.0987.

3-(4-Acetylphenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl 4-methylbenzenesulfonate (3i): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.72–7.66 (m, 2H), 7.58 (d, *J* = 7.3 Hz,1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.40–7.23 (m, 4H), 7.00 (d, *J* = 8.3 Hz,2H), 3.78 (s, 3H), 2.45 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 161.8, 151.2, 145.2, 139.2, 136.5, 135.7, 133.2, 131.9, 131.1, 129.5, 128.0, 127.4, 125.6, 124.0, 122.8, 117.5, 114.0, 30.3, 26.4, 21.5; MS: *m/z* (M^+ + 1) = 448, calcd.: 448; HR-MS: *m/z* = 447.1138, calcd. for $C_{25}H_{21}NO_5S$: 447.1140.

General Procedure for Synthesis of 3,4-Disubstituted Quinolin-2(1*H*)-one 4 or 5

A mixture of **3** (0.20 mmol), Pd $(OAc)_2$ (2.2 mg, 0.01 mmol), ligand **A** (2.5 mg, 0.02 mmol), arylboronic acid, and K_3PO_4 (127 mg, 0.60 mmol) was stirred in *t*-BuOH (2 mL) under nitrogen at 80 °C. The reaction mixture was stirred overnight. Following completion of the reaction as monitored by TLC, the reaction mixture was diluted with ethyl acetate (20 mL) and separated. The solution was dried and filtered, and the filtrate was concentrated to a residue which was purified by flash chromatography [silica gel, 2/1 (v/v) hexane/ethyl acetate] to give the corresponding product **4** or **5**.

4-(4-Methoxyphenyl)-1-methyl-3-phenylquinolin-2(1*H*)-one (4a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (t, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.20–6.09 (m, 6H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 158.8, 147.4, 139.5, 136.1, 132.1, 131.1, 130.6, 130.1, 128.4, 127.4, 126.7, 121.7, 113.9, 113.3, 55.1, 30.0; MS: *m/z* (M^+ + 1) = 342, calcd.: 342; HR-MS: *m/z* = 341.1419, calcd. for $C_{23}H_{19}NO_2$: 341.1416.

1-Methyl-3,4-diphenylquinolin-2(1*H*)-one (4b): ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.57 (t, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.31–7.23 (m, 4H), 7.16–7.08 (m, 8H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 147.7, 139.4, 136.2, 135.8, 131.9, 130.5, 130.2, 129.8, 128.4, 127.9, 127.4, 126.8, 121.8, 121.4, 114.0, 30.0; MS: *m/z* (M^+ + 1) = 312, calcd.: 312; HR-MS: *m/z* = 311.1312, calcd. for $C_{22}H_{17}NO$: 311.1310.

1-Methyl-3-phenyl-4-(4-(trifluoromethyl)phenyl)quinolin-2(1*H*)-one (4c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (t, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.19–7.14 (m, 5H), 7.09–7.06 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 146.1, 140.2, 139.5, 135.3, 132.3, 130.5, 130.4, 130.3, 127.9, 127.6, 127.2, 125.0, 124.4, 122.5, 122.0, 120.8, 114.2, 30.1; MS: *m/z* (M^+ + 1) = 380, calcd.: 380; HR-MS: *m/z* = 379.1180, calcd. for $C_{23}H_{16}F_3NO$: 379.1184.

1-Methyl-3-phenyl-4-(3-(trifluoromethyl)phenyl)quinolin-2(1*H*)-one (4d):[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (t, *J* = 7.3 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.30 (t, *J* = 8.3 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.17–7.05 (m, 8H), 6.99 (s, 1H), 3.85 (s, 3H); MS *m/z* (M^+ + 1) = 380, calcd. for [$C_{23}H_{16}F_3NO$]: 380.

3-(3-Methoxyphenyl)-1-methyl-4-(3-(trifluoromethyl)phenyl)quinolin-2(1*H*)-one (4e):[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (t, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.32 (t, *J* = 8.3 Hz, 1H), 7.26–7.11 (m, 3H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.01–6.98 (m, 3H), 6.71 (d, *J* = 8.8 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): d = 162.0, 158.8, 146.1, 139.8, 137.7, 133.5, 132.6, 132.0, 130.7, 128.9, 128.1, 127.8, 127.2, 127.1, 124.6, 124.5, 122.4, 121.2, 114.5, 113.5, 55.4, 30.4; MS *m/z* (M^+ + 1) = 410, calcd. for [$C_{24}H_{18}F_3NO_2$]: 410.

1-Methyl-3,4-bis(3-(trifluoromethyl)phenyl)quinolin-2(1*H*)-one (4f):[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (t, *J* = 7.3 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.34 (t, *J* = 8.3 Hz, 1H), 7.30–6.99 (m, 7H), 6.95 (s, 1H), 6.88 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.4, 147.2, 140.0, 136.9, 136.4, 134.2, 133.3, 131.4, 131.2, 130.9, 130.5, 130.2, 129.1, 128.3, 127.8, 127.0, 125.0, 124.2, 122.7, 120.9, 114.7, 30.5; MS: *m/z* (M^+ + 1) = 448, calcd. for [$C_{24}H_{15}F_6NO$]: 448.

3,4-Bis(4-methoxyphenyl)-1-methylquinolin-2(1*H*)-one (5a):[22] ^{1}H NMR (400 MHz, $CDCl_3$): d = 7.55 (t, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.04–7.01 (m, 4H), 6.81 (d, *J* = 8.8 Hz,

2H), 6.72 (d, $J=8.8$ Hz, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=162.3$, 159.0, 158.5, 147.5, 139.7, 137.7, 132.1, 132.0, 131.4, 130.3, 129.0, 128.6, 122.1, 122.0, 114.2, 113.7, 113.3, 55.4, 55.3, 30.3; MS: m/z ($M^+ + 1$) = 372, calcd. for $[C_{24}H_{21}NO_3]$: 372.

3,4-Bis(3-cyanophenyl)-1-methylquinolin-2(1*H*)-one (5b):[22] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.68$–7.61 (m, 2H), 7.52–7.31 (m, 9H), 7.21 (t, $J=7.8$ Hz, 1H), 7.15 (d, $J=7.8$ Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=$ 161.1, 146.4, 140.0, 137.3, 136.8, 135.3, 134.4, 133.2, 132.1, 131.8, 131.4, 129.7, 129.0, 128.2, 122.8, 120.5, 118.6, 118.1, 114.8, 113.1, 112.5, 30.5; MS: m/z ($M^+ + 1$) = 362, calcd. for $[C_{24}H_{15}N_3O]$: 362.

Acknowledgements

We thank Professors Xue-Long Hou and Zhen Yang for their invaluable advice during the course of this research. Financial support from National Natural Science Foundation of China (20502004, 20642006) and the Science & Technology Commission of Shanghai Municipality (05ZR14013) is gratefully acknowledged.

References

[1] For examples, see: a) Z. Shi, C. He, *J. Am. Chem. Soc.* **2004**, *126*, 5964; b) Z. Shi, C. He, *J. Org. Chem.* **2004**, *69*, 3669; c) R. Xu, G. Greiveldinger, L. E. Marenus, A. Cooper, J. A. Ellman, *J. Am. Chem. Soc.* **1999**, *121*, 4898; d) P. Wipf, J. T. Reeves, R. Balachandran, K. A. Giuliano, E. Hamel, B. W. Day, *J. Am. Chem. Soc.* **2000**, *122*, 9391; e) D. L. Boger, B. E. Fink, M. P. Hedrick, *J. Am. Chem. Soc.* **2000**, *122*, 6382; f) K. C. Nicolaou, J. A. Pfefferkorn, S. Barluenga, H. J. Mitchell, A. J. Roecker, G.-Q. Cao, *J. Am. Chem. Soc.* **2000**, *122*, 9968, and references cited therein; g) K. R. Roesch, H. Zhang, R. C. Larock, *J. Org. Chem.* **2001**, *66*, 8042; h) K. R. Roesch, R. C. Larock, *J. Org. Chem.* **2002**, *67*, 86, and references cited therein; i) K. R. Roesch, R. C. Larock, *J. Org. Chem.* **2001**, *66*, 412.

[2] P. Ferrer, C. Avendaño, M. Söllhuber, *Liebigs Ann.* **1995**, 1895.

[3] a) A. L. Hopkins, J. Ren, J. Milton, R. J. Hazen, J. H. Chan, D. I. Stuart, D. K. Stammers, *J. Med. Chem.* **2004**, *47*, 5912; b) G. A. Freeman, C. W. Andrews III, A. L. Hopkins, G. S. Lowell, L. T. Schaller, J. R. Cowan, S. S. Gonzales, G. W. Koszalka, R. J. Hazen, L. R. Boone, R. G. Ferris, K. L. Creech, G. B. Roberts, S. A. Short, K. Weaver, D. J. Reynolds, J. Milton, J. Ren, D. I. Stuart, D. K. Stammers, J. H. Chan, *J. Med. Chem.* **2004**, *47*, 5923.

[4] a) M. Anzini, A. Cappelli, S. Vomero, *J. Heterocycl. Chem.* **1991**, *28*, 1809; b) A. Godard, J. M. Fourquez, R. Tamion, F. Marsais, G. Quéguiner, *Synlett* **1994**, 235.

[5] a) J. Wu, L. Zhang, K. Gao, *Eur. J. Org. Chem.* **2006**, 5260; b) J. Wu, L. Zhang, H.-G. Xia, *Tetrahedron Lett.* **2006**, *47*, 1525; c) J. Wu, L. Zhang, Y. Luo, *Tetrahedron Lett.* **2006**, *47*, 6747; d) J. Wu, X. Sun, L. Zhang, *Chem. Lett.* **2005**, *34*, 796; e) J. Wu, Q. Zhu, L. Wang, R. Fathi, Z. Yang, *J. Org. Chem.* **2003**, *68*, 670; f) J. Wu, L. Wang, R. Fathi, Z. Yang, *Tetrahedron Lett.* **2002**, *43*, 3395; g) J. Wu, Y. Liao, Z. Yang, *J. Org. Chem.* **2001**, *66*, 3642.

[6] For some recent examples of regioselective cross-coupling reactions, see: a) M. Hocek, D. Hockova, H. Dvorakova, *Synthesis* **2004**, 889; b) M. Hocek, I. Votruba, H. Dvorakova, *Tetrahedron* **2003**, *59*, 607; c) T. Bach, S. Heuser, *J. Org. Chem.* **2002**, *67*, 5789; d) T. Bach, S. Heuser, *Angew. Chem. Int. Ed.* **2001**, *40*, 3184; e) F. Bellina, C. Anselmi, R. Rossi, *Tetrahedron Lett.* **2001**, *42*, 3851.

[7] G. Jones, (Ed.), *Quinolines*, John Wiley & Sons, London, New York, Sydney, Toronto, **1977**, pp 181–187.

[8] G. Jones, (Ed.), *Quinolines*, John Wiley & Sons, London, New York, Sydney, Toronto, **1977**, pp 191–194.

[9] <G. Jones, (Ed.), *Quinolines*, John Wiley & Sons, London, New York, Sydney, Toronto, **1977**, pp 151–158.

[10] a) A. L. Searles, D. Ressler, *J. Am. Chem. Soc.* **1958**, *80*, 3656; b) K. K. Park, J. J. Lee, *Tetrahedron* **2004**, *60*, 2993.

[11] A. Fürstner, D. N. Jumbam, N. Shi, *Z. Naturforsch. B* **1995**, *50*, 326.

[12] G. Merault, P. Bougeois, N. Duffaut, *Bull. Soc. Chim. Fr.* **1974**, 1949.

[13] K. Kobayashi, T. Kitamura, K. Yoneda, O. Morikawa, H. Konishi, *Chem. Lett.* **2000**, 798.

[14] N. A. Cortese, C. B., Jr. Ziegler, B. J. Hrnjez, R. F. Heck, *J. Org. Chem.* **1978**, *43*, 2952.

[15] C. W. Holzapfel, C. Dwyer, *Heterocycles* **1998**, *48*, 215.

[16] M. Mori, K. Chiba, N. Ohta, Y. Ban, *Heterocycles* **1979**, *13*, 329.

[17] D. V. Kadnikov, R. C. Larock, *J. Org. Chem.* **2004**, *69*, 6772 and references cited therein.

[18] D. Yang, Y.-L. Yan, B. Lui, *J. Org. Chem.* **2002**, *67*, 7429.

[19] a) Z.-Y. Tang, Q.-S. Hu, *J. Am. Chem. Soc.* **2004**, *126*, 3058; b) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818 and references cited therein.

[20] For recent reviews, see: a) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11; b) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; c) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

[21] S. Wolfgang, *Monatshefte. fuer. Chemie.* **1986**, 117, 1305.

[22] J. Wu, L. Zhang, X. Sun, *Chem. Lett.* **2005**, 34, 550.

