JOC The Journal of Organic Chemistry

Note

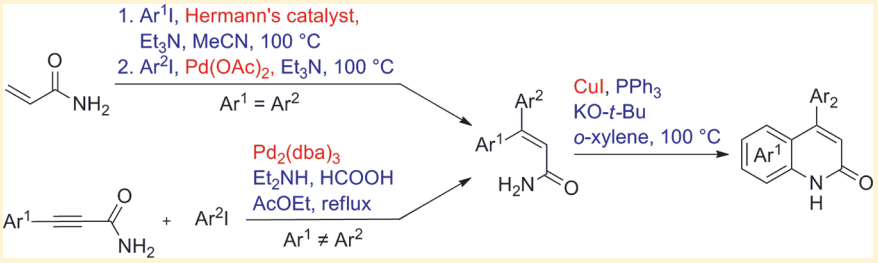
pubs.acs.org/joc

4-Aryl-2-quinolones from 3,3-Diarylacrylamides through Intramolecular Copper-Catalyzed C−H Functionalization/C−N Bond Formation

Roberta Berrino, Sandro Cacchi,* Giancarlo Fabrizi, and Antonella Goggiamani

Dipartimento di Chimica e Tecnologie del Farmaco, La Sapienza, Università di Roma, P. le A. Moro 5, 00185 Rome, Italy

Supporting Information

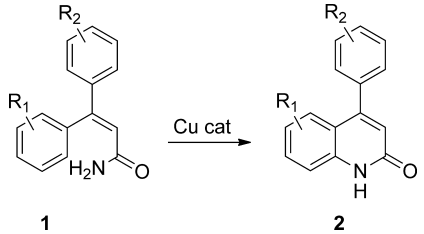


ABSTRACT: Free NH 3,3-diarylacrylamides are cyclized to substituted 2-quinolones in the presence of CuI, PPh_3, and KO-*t*-Bu in *o*-xylene at 100 °C. The reaction proceeds through a C−H functionalization/C−N bond formation process. With unsymmetrical 3,3-diarylacrylamides, high selectivity is observed using substrates where the aromatic ring *trans* to the amide group bears *o*-methyl, -chloro, or -bromo substituents.

In recent years, direct transition-metal-catalyzed functionalization reactions of (hetero)arenes through the activation of inert C−H bonds, for the most part involving palladium-, rhodium-, and ruthenium-based catalysts, has been intensively investigated.[1−3] Several reports have shown the potential of this chemistry as an attractive, greener alternative to the more commonly employed cross-coupling reactions using preactivated (hetero)arenes (usually halo derivatives). More recently, because of the economic advantages and good functional tolerance of copper-catalyzed methods, several groups have dedicated a growing attention to the use of copper catalysis[4,5] in the formation of C−C,[6−12] C−N,[13−20] C−O,[21−23] and C−Cl[21] bonds via catalytic functionalization of (hetero)aryl C−H bonds.

Herein we report on a new synthesis of 4-aryl-2-quinolones from free NH 3,3-diarylacrylamides that involves an intramolecular copper-catalyzed aryl C−H functionalization through C−N bond formation (Scheme 1).

Scheme 1. Copper-Catalyzed Construction of the 2-Quinolone Ring from 3,3-Diarylacrylamides



1 2

2-Quinolone subunits are prevalent in a vast array of biologically active compounds.[24−26] The 4-aryl-2-quinolone derivative tipifarnib exhibits anticancer activity.[27] Furthermore, 2-quinolones are useful synthetic intermediates.[28] Consequently, several methods for the construction of the 2-quinolone ring have been developed.[29] However, relatively few of them are based on transition-metal catalysis and palladium catalysis plays a major role.[30−34] To the best of our knowledge, only one example of a copper-catalyzed approach to this class of compounds was described.[35] In that case, the 2-quinolone scaffold was prepared via cyclization of acrylamides bearing a *β*-aryl group containing an ortho bromo substituent, a process requiring a preactivated arene that can react selectively with the metal catalyst. Thus, the development of new transition-metal-catalyzed procedures is a subject of great interest, particularly when they do not need wasteful preactivation steps, are based on simple protocols, inexpensive catalyst systems, and readily available starting materials.

The starting 3,3-diarylacrylamides **1** were prepared via Heck reaction of cinnamylamides with aryl iodides[35] or hydroarylation of 3-arylpropiolamides with aryl iodides.[36]

We started our study by examining the conversion of 3,3-diphenylacrylamide **1a** ($R^1 = R^2 = H$) into the corresponding quinolone **2a**. Cyclization reactions were typically carried out under an atmosphere of air. After an initial screen of copper-based catalysts [CuI/L-proline,[37] $Cu(OTf)_2$, $Cu(OAc)_2/PPh_3$, $CuNO_3(PPh_3)_2$, $CuNO_3$(1,10-phenanthroline)$(PPh_3)_2$,[38] CuI/

Received: December 13, 2011
Published: January 24, 2012

1,10-phenanthroline, CuI/pyridine], solvents (DMF, toluene, xylene), bases (KO-*t*-Bu, K_2CO_3, Na_2CO_3, Cs_2CO_3, NaH), and reaction temperatures (100−140 °C), we found that **2a** could be isolated in 75% yield by using 0.1 equiv of recrystallized CuI[39] and 0.2 equiv of PPh_3 in the presence of 2 equiv of KO-*t*-Bu in *o*-xylene at 100 °C after 5 h under aerobic conditions. Benzophenone was isolated in 8% yield. Most probably, its formation involves a copper-catalyzed oxidative cleavage of the carbon−carbon double bond,[40] a reaction that is favored by molecular oxygen. Accordingly, **2a** and benzophenone were isolated in 50 and 20% yield, respectively, when **1a** was subjected to CuI under the above-mentioned conditions for 24 h under a balloon of molecular oxygen. To prevent this side reaction, we then attempted the cyclization under an atmosphere of nitrogen. However, **2a** was isolated only in 15% yield, and the starting material was recovered in 61% yield. These results imply that an excess of oxygen is detrimental to the reaction increasing the amount of benzophenone. Nevertheless, oxygen is needed to get the best results, most probably acting in reoxidation steps that involve the copper catalyst.

Therefore, when the method was extended to the preparation of other quinolone derivatives, we decided to carry out the reactions under an atmosphere of air, the simplest way to reach a satisfactory concentration of oxygen.

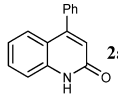
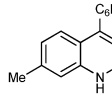
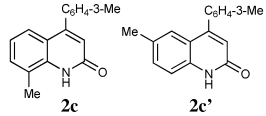
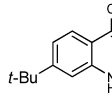
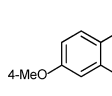
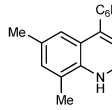
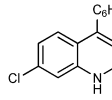
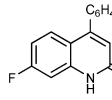
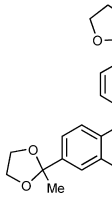
As shown in Table 1, moderate to high yields of the desired products were obtained from symmetrical 3,3-diarylacrylamides ($R^1 = R^2$) bearing neutral, electron-rich, and moderately electron-poor aromatic rings. No evidence of 2-quinolone formation was obtained in the presence of strongly electron-withdrawing groups (Table 1, entry 9), suggesting that the nucleophilicity of the aromatic ring plays a key role in the cyclization event. Accordingly, an acrylamide containing appropriately protected ketone groups on the 3-aryl rings gave the desired product in good yield (Table 1, entry 10). The presence of substituents at both meta positions of the aromatic fragment does not hamper the reaction (Table 1, entry 6). When there is only one meta substituent, the cyclization affords regioisomeric derivatives (Table 1, entry 3).

We next explored the cyclization of unsymmetrical 3,3-diarylacrylamides ($R^1 \neq R^2$). Rather disappointingly, both the substrates **1k** and its diastereoisomer **1k′**, selected as model systems, afforded mixtures of isomeric quinolones (Scheme 2). Compound **1k** gave an almost equimolar amount of **2k** and **3k** in high overall yield, whereas a high selectivity was observed with **1k′** but **2k** and **3k** were isolated in low overall yield. The low overall yield of the isomeric quinolones in the cyclization of **1k′** is due to its the strong tendency (higher than that of **1k**) to undergo the oxidative cleavage of the carbon−carbon double bond. The substrate **1k** afforded a 18% yield of the corresponding benzophenone whereas the latter was isolated in 45% yield starting from **1k′**. The reasons for this behavior are unclear at the moment.

A couple of considerations can be drawn from these results. The first one is that an *E*/*Z* isomerization of the starting acrylamides is likely to take place under the reaction conditions. This notion is supported by the recovery of the starting material **1k′** and its diastereoisomer **1k** in 13% overall yield as an approximately 87:13 **1k′**/**1k** mixture when the cyclization of **1k′** was attempted. Control experiments revealed that the isomerization is due to the presence of KO-*t*-Bu. Indeed, an approximately 85:15 **1k′**/**1k** mixture is formed upon treatment of **1k′** with KO-*t*-Bu in *o*-xylene omitting CuI and PPh_3 after 24 h at 100 °C. No isomerization was observed when **1k′** was subjected to CuI and PPh_3 in xylene at 100 °C for 24 h in the absence of KO-*t*-Bu.

The second one is that the ratio between the isomeric quinolone products appears to depend on a subtle balance between the equilibration and the cyclization rate, the latter in turn depending on the nature of the substituents on the aromatic rings. With **1k′**, the cyclization reaction is faster than the equilibration reaction. As a consequence, a good **3k**:**2k** ratio is observed. In the cyclization of **1k**, the lower reactivity (as compared to that of the phenyl ring) of the aromatic ring bearing a methoxy group meta to the carbon involved in the copper-catalyzed C−N bond formation makes it the cyclization rate comparable to (or lower than) the equilibration rate and the isomeric quinolones are obtained in an approximately 1:1 ratio.

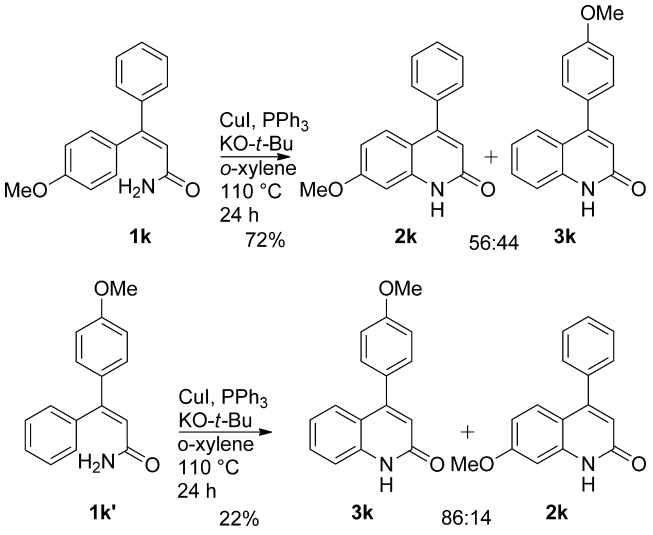
Table 1. Copper-Catalyzed Synthesis of 4-Arylquinolones from Symmetrical 3,3-Diarylacrylamides[a]

Entry	3,3-Diarylacrylamide **1** $R^1 = R^2$		T (h)	Product (Yield %)[b]
1	H	**1a**	5	 **2a** (75)
2	4-Me	**1b**	24	 **2b** (57)
3	3-Me	**1c**	24	 **2c** **2c'** (63) **2c**:**2c'** = 70:30
4	4-*t*-Bu	**1d**	24	 **2d** (76)
5	4-MeO	**1e**	8	 **2e** (62)
6	3,5-Me_2	**1f**	24	 **2f** (72)
7	4-Cl	**1g**	8	 **2g** (62)
8	4-F	**1h**	24	 **2h** (41)
9	4-CO_2Et	**1i**	24	-
10		**1j**	24	 **2j** (41)

[a]Unless otherwise stated, reactions were carried out under an atmosphere of air on a 0.45 mmol scale at 100 °C using 0.1 equiv of recrystallized CuI, 0.2 equiv of PPh_3, and 2 equiv of KO-*t*-Bu in 3 mL of *o*-xylene. [b]Yields are given for isolated products.

dx.doi.org/10.1021/jo202427m | *J. Org. Chem.* 2012, 77, 2537−2542

Scheme 2. Copper-Catalyzed Cyclization of Unsymmetrical 3,3-Diarylacrylamides 1k and 1k′



On the basis of these results, we hypothesized that slowing down the equilibration rate by an appropriate choice of the substituents at the aromatic rings might produce a highly selective cyclization process. Further investigations on the reactivity of unsymmetrical substrates revealed that such a selective cyclization process could be achieved by taking advantage of the steric effects[41] of the substituents on the aromatic rings.

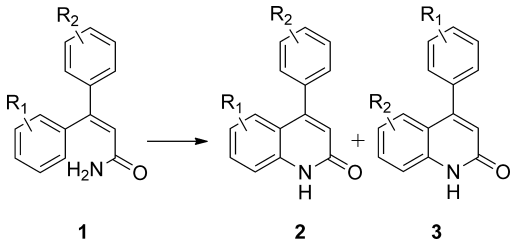
In particular, the substrate **1m**, a 3,3-diarylacrylamide containing an *o*-methyl group on the aromatic ring *trans* to the amide group, was found to possess a strong tendency to preserve its configuration under the reaction conditions. Indeed, the quinolone product was obtained in acceptable yield and high **2m**/**3m** ratio when the cyclization of **1m** was attempted (Table 2, entry 1). The starting acrylamide was recovered along with its diastereoisomer **1m′** (containing the ortho substituted aromatic ring on the same side of the carbon−carbon double bond as the amide group) in an overall 18% yield as an approximately 91:9 mixture.

Control experiments revealed that treatment of **1m** with KO-*t*-Bu in *o*-xylene omitting CuI and PPh_3 affords an approximately 93:7 **1m**/**1m′** mixture after 24 h at 100 °C whereas an approximately 94:6 **1m′**/**1m** mixture is obtained from its diastereoisomer **1m′** under the same conditions. These data support the notion that with ortho substituted 3,3-diarylacrylamides the composition of the quinolone mixture is mostly dependent on a relatively high energy barrier for the *E*/*Z* isomerization.

Building on the reactivity of **1m**—with the idea of exploiting the effect of ortho substituents to develop a highly selective synthesis and, at the same time, providing a route to quinolones that might allow for increasing their molecular complexity via transition-metal-catalyzed coupling reactions—we explored the use of substrates bearing 3-(*o*-chlorophenyl)- and 3-(*o*-bromophenyl)- substituents *trans* to the amide group. To our delight, these substrates underwent selectively the cyclization to the corresponding quinolones in acceptable to high yields (Table 2, entries 2−7). The cyclization of **1q** (Table 2, entry 7) is of particular interest in that the contemporary presence of chloro and bromo substituents in the quinolone product may pave the way to selective double functionalizations (C−Cl and C−Br bonds show different reactivity in oxidative additions to transition metals).

On the basis of the above results and literature precedent of related processes,[10,13,18] a possible rationale for the copper-catalyzed synthesis of 2-quinolones from 3,3-diarylacrylamides is outlined in Scheme 3.[42] The reaction of the acrylamide **1** with the copper salt under basic conditions (pathway *a*) is expected to afford the intermediate **A** that is converted to **B** upon oxidation. A subsequent intramolecular electrophilic attack to the aromatic ring produces **C**. Base-promoted rearomatization generates **D** from which the quinolone product **2** is formed via reductive elimination with the catalyst regenerated by oxidation.[43,44] Alternatively (pathway b), oxidation of Cu(I) to Cu(II) can take place. The reaction of **1** with Cu(II) under basic conditions affords **B**.

Table 2. Copper-Catalyzed Cyclization of Unsymmetrical 3,3-Diarylacrylamides[a]

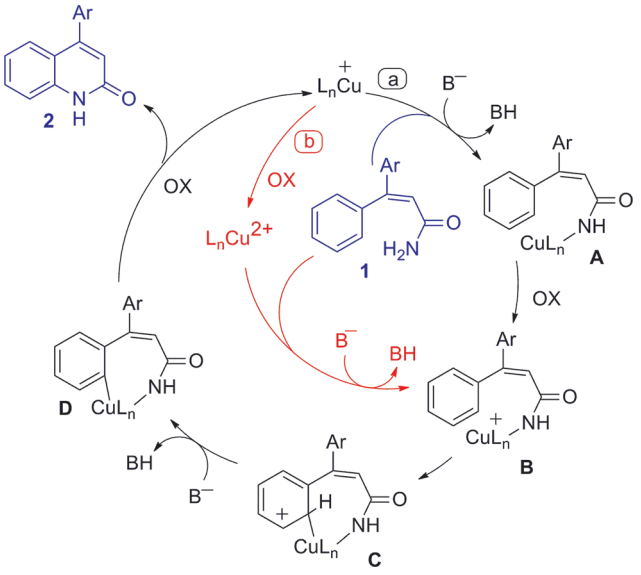


	3,3-diarylacrylamide **1**				
entry	R^1	R^2		overall yield[b] (%)	**2**/**3** ratio[c]
1	4-F	2-Me	**1m**	50	**2m**/**3m** = 96:4
2	H	2-Cl	**1n**	75	**2n**/**3n** = 92:8
3	4-MeO	2-Cl	**1o**	63	**2o**/**3o** > 99:1
4	4-Me	2-Cl	**1p**	61	**2p**/**3p** = 97:3
5	4-Br	2-Cl	**1q**	43	**2q**/**3q** > 99:1
6	4-F	2-Cl	**1r**	41	**2r**/**3r** > 99:1
7	4-Me	2-Br	**1s**	53	**2s**/**3s** > 99:1

[a]Unless otherwise stated, reactions were carried out under an atmosphere of air on a 0.45 mmol scale at 100 °C for 24 h using 0.1 equiv of recrystallized CuI, 0.2 equiv of PPh_3, and 2 equiv of KO-*t*-Bu in 3 mL of *o*-xylene. [b]Yields are given for isolated products. [c]Molar ratios were determined by NMR analysis.

dx.doi.org/10.1021/jo202427m | J. Org. Chem. 2012, 77, 2537−2542

Scheme 3. Proposed Mechanism



In summary, we have developed a novel copper-catalyzed approach for the construction of the 2-quinolone ring from free NH 3,3-diarylacrylamides that is based on an intramolecular C−H functionalization/C−N bond forming process. With unsymmetrical 3,3-diarylacrylamides high selectivity is observed using substrates where the aromatic ring *trans* to the amide group bears *o*-methyl, -chloro, or -bromo substituents. Our procedure is simple, uses readily available starting materials and an inexpensive catalyst system. Although moderate yields are obtained in some cases, it can be a useful complement to commonly used strategies.

EXPERIMENTAL SECTION

Melting points are uncorrected. All of the reagents, catalysts, and solvents are commercially available and were used as purchased, without further purification. CuI used in the general procedure was recrystallized according to literature.[39] Reaction products were purified by flash column chromatography using SiO_2 25−40 μm and eluting with *n*-hexane/ethyl acetate/methanol mixtures. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively.

Typical Procedure for the Preparation of Symmetrical 3,3-Diarylacrylamides: 3,3-Diphenylacrylamide (1a). To a stirred solution of acrylamide (1.0 g, 13.9 mmol) in MeCN (10.0 mL), iodobenzene (1.71 mL, 15.3 mmol), and Et_3N (5.79 mL, 41.7 mmol) was added Hermann's catalyst (130.2 mg, 0.139 mmol). The reaction mixture was stirred overnight at 100 °C. After this time, the reaction mixture was cooled, diluted with EtOAc, and washed with HCl 2 N, a saturated $NaHCO_3$ solution, and finally brine. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in Et_3N (10 mL), iodobenzene (2.33 mL, 20.86 mmol) and $Pd(OAc)_2$ (156.0 mg, 0.695 mmol) were added, and the resulting reaction mixture was stirred overnight at 100 °C. After this time, the reaction mixture was cooled, diluted with EtOAc, and washed with HCl 2 N, a saturated $NaHCO_3$ solution, and finally brine. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by chromatography (silica gel, 40/60 v/v *n*-hexane/AcOEt) to give 2.67 g (86% yield) of **1a**: white solid; mp 147−151 °C (lit.[39] mp 150−153 °C); IR (KBr) 3285, 1654, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46−7.44 (m, 3H), 7.38−7.28 (m, 7 H), 6.41 (s, 1 H), 5.99 (br s, 1 H), 5.24 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.5, 151.0, 140.5, 138.0, 129.2, 129.0, 128.8, 128.7, 128.3, 127.9, 121.7. Anal. Calcd for $C_{15}H_{13}$ NO: C, 80.69; H, 5.87. Found: C, 80.96; H, 5.85.

Typical Procedure for the Preparation of Unsymmetrical 3,3-Diarylacrylamides: (*Z*)-3-(4-Methoxyphenyl)-3-phenylacrylamide (1k). 3-(4-Methoxyphenyl)propiolamide (175.2 mg, 1 mmol), iodobenzene (0.22 mL, 2 mmol), and $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol) were dissolved in AcOEt (50 mL). Et_2NH (0.31 mL, 3 mmol) was added, followed by HCO_2H (0.08 mL, 2 mmol), and the solution was heated to reflux until reaction completion. The reaction mixture was then cooled to room temperature and washed with HCl 2 N, a saturated $NaHCO_3$ solution, and finally brine. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; 20/80 v/v *n*-hexane/AcOEt) to give 177.1 mg (70% yield) of **1k**: yellow solid; mp 164−166 °C; IR (KBr) 3234, 1680, 1597, 1422, 1164, 1082 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36−7.24 (m, 7H), 6.98 (m, J = 8.4 Hz, 2 H), 6.34 (s, 1 H), 5.41 (br s, 1 H), 5.17 (br s, 1 H), 3.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.6, 151.2, 140.7, 138.6, 135.2, 129.6, 129.2, 128.4, 128.0, 121.6, 55.5. Anal. Calcd for $C_{16}H_{15}$ NO_2: C, 75.87; H, 5.97 97. Found: C, 76.09; H, 5.96.

Typical Procedure for the Preparation of 2: 4-Phenylquinolin-2(1*H*)-one (2a). To a stirred solution of CuI (8.6 mg, 0.05 mmol) and PPh_3 (23.6 mg, 0.09 mmol) in 1.0 mL of anhydrous *o*-xylene were added 3,3-diarylacrylamide **1a** (99.5 mg, 0.45 mmol) and KO-*t*-Bu (101.0 mg, 0.90 mmol) at room temperature with 2.0 mL of the solvent. Then the mixture was stirred for 24 h at 100 °C. After this time, the reaction mixture was cooled to room temperature, diluted with AcOEt, and washed with brine. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, *n*-hexane/AcOEt 15/85 v/v) to afford 66.3 mg (75% yield) of **2a**: white solid; mp 262−264 °C (lit.[33] mp 259−260 °C); IR (KBr) 2954, 1654 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.91 (br s, 1 H), 7.56−7.47 (m, 6 H), 7.42−7.37 (m, 2 H), 7.17−7.13 (m, 1 H), 6.40 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 161.8, 151.9, 139.8, 137.2, 131.0, 129.2, 129.16, 129.14, 126.6, 122.3, 121.7, 118.8, 116.3. Anal. Calcd for $C_{15}H_{11}$ NO: C, 81.43; H, 5.01. Found: C, 81.52; H, 4.99.

7-Methyl-4-*p*-tolylquinolin-2(1*H*)-one (2b): yellow solid; mp 193−195 °C; IR (KBr) 3450, 1655 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 11.76 (br s, 1 H); 7.35 (s, 4 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.19 (s, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 6.29 (s, 1 H), 2.40 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 162.0, 151.9, 141.1, 139.9, 138.7, 134.4, 129.7, 128.9, 126.5, 123.7, 120.3, 116.8, 115.9, 21.6, 21.3. Anal. Calcd for $C_{17}H_{15}$NO: C, 81.90; H, 6.06. Found: C, 81.87; H, 6.07.

8-Methyl-4-*m*-tolylquinolin-2(1*H*)-one (2c) and 6-Methyl-4-*m*-tolylquinolin-2(1*H*)-one (2c′). The two regioisomeric quinolones were obtained in a 70:30 molar ratio. The ratio of two isomers was determined by ^{1}H NMR; they were separated by semipreparative HPLC. **2c**: yellow solid; mp 204−207 °C; IR (KBr) 2983, 1656 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.95 (br s, 1 H), 7.44−7.38 (m, 2 H), 7.32 (d, J = 7.6 Hz, 1 H), 7.26−7.21 (m, 3 H) 7.05 (t, J = 7.6 Hz, 1 H), 6.38 (s, 1 H), 2.48 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 162.1, 152.6, 138.4, 138.0, 137.5, 132.3, 129.8, 129.6, 128.9, 126.2, 124.8, 124.4, 121.9, 121.3, 119.1, 21.4, 17.9. Anal. Calcd for $C_{17}H_{15}$NO, C, 81.90; H, 6.06. Found: C, 81.93; H, 6.07. **2c′**: yellow solid; mp 212−215 °C; IR (KBr) 2986, 1565 cm^{-1}; ^{1}H NMR (400 MHz) (DMSO-d_6) δ 11.78 (br s, 1 H); 7.45−7.41 (m, 1 H), 7.37−7.21 (m, 6 H), 6.33 (s, 1 H), 2.40 (s, 3 H), 2.26 (s, 3 H); ^{13}C NMR (100.6 MHz) (DMSO-d_6) δ 161.6, 151.9, 138.5, 137.8, 137.3, 132.2, 131.2, 129.8, 129.6, 128.9, 126.2, 126.1, 121.6, 118.8, 116.2, 21.5, 21.1. Anal. Calcd for $C_{17}H_{15}$NO: C, 81.90; H, 6.06. Found: C, 81.87; H, 6.07.

7-*tert*-Butyl-4-(4-*tert*-butylphenyl)quinolin-2(1*H*)-one (2d): yellow solid; mp 289−291 °C; IR (KBr) 2962, 1656, 1621 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.57 (br s, 1 H), 7.59−7.44 (m, 6 H), 7.26−7.23 (m, 1 H), 6.71 (s, 1 H), 1.43 (s, 9 H), 1.40 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 166.7, 154.5, 151.8, 139.0, 134.5, 128.6, 126.5, 125.5, 120.4, 117.5, 112.9, 35.0, 34.8, 31.4, 31.1. Anal. Calcd for $C_{23}H_{27}$NO: C, 82.84; H, 8.16. Found: C, 82.73; H, 8.17.

7-Methoxy-4-(4-methoxyphenyl)quinolin-2(1*H*)-one (2e): white solid;[39] mp 229−232 °C; IR (KBr) 3448, 1654, 1608, 1216 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.68 (br s, 1 H), 7.41 (d, J = 8.8 Hz, 2 H), 7.35 (d, J = 9.2 Hz, 1 H), 7.09 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 2.0

dx.doi.org/10.1021/jo202427m | *J. Org. Chem.* 2012, 77, 2537−2542

Hz, 1 H), 6.77 (dd, J_1 = 9.2 Hz, J_2 = 2.0 Hz 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 162.2, 161.5, 160.1, 151.6, 141.6, 130.4, 129.6, 128.1, 118.3, 114.6, 113.1, 110.1, 99.0, 55.8, 55.7. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37. Found: C, 72.44; H, 5.38.

4-(3,5-Dimethylphenyl)-6,8-dimethylquinolin-2(1*H*)-one (2f): white solid; mp 235−239 °C; IR (KBr) 3565, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.32 (br s, 1 H), 7.20 (d, J = 10.4 Hz, 2 H), 7.14 (s, 1 H), 7.05 (s, 1 H), 6.58 (s, 1 H), 2.51 (s, 3 H), 2.42 (s, 6 H), 2.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.8, 153.7, 138.1, 137.6, 135.2, 133.3, 131.3, 130.2, 126.6, 125.8, 124.8, 123.3, 119.7, 21.4, 17.1. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90. Found: C, 81.99; H, 6.92.

7-Chloro-4-(4-chlorophenyl)quinolin-2(1*H*)-one (2g): white solid;[33] mp 270−274 °C; IR (KBr) 3448, 1673 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.03 (br s, 1 H), 7.62 (d, J = 8.4 Hz, 2 H), 7.52 (d, J = 8.4 Hz, 2 H), 7.44 (d, J = 2.4 Hz, 1 H), 7.36 (d, J = 8.8 Hz, 1 H), 7.20 (dd, J_1 = 8.8 Hz, J_2 = 2.2 Hz 1 H), 6.45 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 161.6, 150.2, 140.7, 135.6, 134.3, 131.07, 131.06, 129.3, 128.4, 122.5, 122.2, 117.6, 115.4. Anal. Calcd for $C_{15}H_9Cl_2NO$: C, 62.09; H, 3.13. Found: C, 62.16; H, 3.11.

7-Fluoro-4-(4-fluorophenyl)quinolin-2(1*H*)-one (2h): yellow solid;[39] mp 302−306 °C; IR (KBr) 2981, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.65 (br s, 1 H), 7.54−7.45 (m, 3 H), 7.27−7.22 (m, 3 H), 6.94 (ddt, J_1 = 8.8 Hz, J_2 = 2.4 Hz, J_3 = 0.8 Hz, 1 H), 6.63 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 164.2, 164.1 (d, J = 250.6 Hz), 163.2 (d, J = 249.3 Hz), 152.1, 140.5 (d, J = 12.1 Hz), 132.9 (d, J = 3.3 Hz), 130.6 (d, J = 8.3 Hz), 128.9 (d, J = 10.2 Hz), 119.9 (d, J = 3.4 Hz), 116.3 (d, J = 2.6 Hz), 115.9 (d, J = 21.7 Hz), 111.2 (d, J = 23.0 Hz), 102.7 (d, J = 25.0 Hz); ^{19}F NMR (376.5 MHz) δ −107.6, −112.1. Anal. Calcd for $C_{15}H_9F_2NO$: C, 70.04; H, 3.53. Found: C, 70.21; H, 3.52.

7-(2-Methyl-1,3-dioxolan-2-yl)-4-(2-methyl-1,3-dioxolan-2-yl)phenyl)quinolin-2(1*H*)-one (2j): white solid; mp 272−275 °C; IR (neat) 2985, 1654, 1124, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.80 (br s, 1 H), 7.66 (d, J = 8.4 Hz, 2 H), 7.57 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2 H), 7.30 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz 1 H), 6.69 (s, 1 H), 4.17−4.05 (m, 4 H), 3.95−3.79 (m, 4 H), 1.76 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.6, 152.8, 146.7, 144.2, 138.8, 136.6, 128.7, 127.0, 125.6, 119.9, 119.1, 113.0, 108.7, 108.4, 64.7, 27.6, 27.5. Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89. Found: C, 70.34; H, 5.87.

7-Methoxy-4-phenylquinolin-2(1*H*)-one (2k): yellow solid;[39] mp 234−237 °C; IR (KBr) 2910, 1654, 1610, 1220 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.75 (br s, 1H), 7.54−7.51 (m, 3 H), 7.46−7−44 (m, 2 H), 7.28 (d, J = 9.2 Hz, 1 H), 6.91 (d, J = 2.8 Hz, 1 H), 6.77 (dd, J_1 = 9.2, J_2 = 2.8 Hz, 1 H), 6.22 (s, 1 H), 3.82 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 162.2, 161.5, 151.9, 141.6, 137.5, 129.2, 129.1, 129.0, 128.1, 118.5, 112.9, 111.2, 98.9, 55.9. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. Found: C, 76,40; H, 5.23.

4-(4-Methoxyphenyl)quinolin-2(1*H*)-one (3k): yellow solid;[39] mp 228−231 °C IR (KBr) 2910, 1654, 1610, 1220 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.84 (br s, 1H), 7.55−7.51 (m, 1 H), 7.46−7−39 (m, 4 H), 7.17−7.10 (m, 3 H), 6.37 (d, 1 H), 3.84 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 161.9, 160.1, 151.7, 139.8, 130.9, 130.5, 129.3, 126.7, 122.2, 121.4, 119.0, 116.2, 114.6, 55.7. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. Found: C, 76,51; H, 5.20.

7-Fluoro-4-*o*-tolylquinolin-2(1*H*)-one (2m) and 4-(4-Fluorophenyl)-5-methylquinolin-2(1*H*)-one (3m). Obtained as a mixture of two isomers. The ratio of two isomers was determined by ^{1}H NMR as **2m**/**3m** = 96:4.Compound **2m** could be separated from the mixture by semipreparative HPLC: white solid; mp 171−174 °C; IR (KBr) 3340, 1675, 1542 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.12 (br s, 1 H), 7.44−7.22 (m, 5 H), 7.16−7.12 (m, 1 H), 6.89−6.85 (m, 1 H), 6.61 (s, 1 H), 2.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.9, 164.8, 164.1 (d, J = 250.0 Hz), 153.4, 140.1 (d, J = 11.8 Hz), 136.4, 135.5, 130.4, 128.9 (d, J = 9.6 Hz), 128.8, 126.0, 119.8, 116.9, 111.3 (d, J = 23.2 Hz), 102.7 (d, J = 25.2 Hz), 19.8; ^{19}F NMR (376.5 MHz) δ −107.8. Anal. Calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78. Found: C, 75.83; H, 4.80.

4-(2-Chlorophenyl)quinolin-2(1*H*)-one (2n) and 5-Chloro-4-phenylquinolin-2-(1*H*)-one (3n). Obtained as a mixture of two isomers. The ratio of two isomers was determined by ^{1}H NMR as **2n**/**3n** = 92:8. Compound **2n** could be separated from the mixture by semipreparative HPLC: white solid; mp 213−216 °C; IR (KBr) 3386, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.02 (br s, 1 H), 7.61−7.53 (m, 3 H), 7−49−7−36 (m, 3 H), 7.20−7.14 (m, 2 H), 6.72 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 164.2, 151.0, 138.6, 135.9, 132.9, 130.8, 130.7, 130.1, 129.9, 126.9, 126.5, 122.7, 121.7, 119.5, 116.7. Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94. Found: C, 70.29; H, 3.96.

4-(2-Chlorophenyl)-7-methoxyquinolin-2(1*H*)-one (2o): yellow solid; mp 189−192 °C; IR (KBr) 3415, 2235, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.59 (br s, 1 H), 7.55 (d, J = 7.2 Hz, 1 H), 7.49−7.39 (m, 2 H), 7.34 (dd, J_1 = 7.6, J_2 = 1.2 Hz, 1 H), 7.06 (d, J = 8.8 Hz, 1 H), 6.94 (s, 1 H), 6.76 (dd, J_1 = 8.8, J_2 = 2.0 Hz, 1 H), 6.52 (s,1 H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.0, 150.9, 140.3, 136.2, 132.8, 130.6, 129.9, 129.8, 127.9, 126.9, 118.5, 113.7, 112.6, 98.6, 55.7. Anal. Calcd for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23. Found: C, 67.32; H, 4.21.

4-(2-Chlorophenyl)-7-methylquinolin-2(1*H*)-one (2p) and 5-Chloro-4-*p*-tolylquinolin-2-(1*H*)-one (3p). Obtained as a mixture of two isomers. The ratio of two isomers was determined by ^{1}H NMR spectrum as **2p**/**3p** = 97:3. Compound **2p** could be separated from the mixture by semipreparative HPLC: yellow solid; mp 210−212 °C; IR (KBr) 3450, 1665, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.89 (br s, 1H) 7.58−7.55 (m, 1 H), 7.48−7.40 (m, 2 H), 7.38−7.35 (m, 2 H), 7.06 (d, J = 8.0 Hz, 1 H), 6.98 (dd, J_1 = 8.4, J_2 = 1.2 Hz, 1 H), 6.65 (s, 1 H), 2.48 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.4, 150.9, 141.8, 138.7, 136.1, 132.9, 130.6, 130.0, 129.9, 126.9, 126.3, 124.4, 120.5, 117.4, 116.4, 21.6. Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48. Found: C, 71.22; H, 4.49.

7-Bromo-4-(2-chlorophenyl)quinolin-2(1*H*)-one (2q): yellow solid; mp 231−235 °C; IR (KBr) 3378, 2334, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.01 (br s, 1 H), 7.74 (s, 1 H), 7.57 (d, J = 7.6, 1 H), 7.49−7.42 (m, 2 H), 7.36 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.27 (dd, J_1 = 8.8 Hz, J_2 = 1.2 Hz, 1 H) 7.034 (d, J = 8.8, 1 H), 6.67 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 164.2, 150.7, 139.3, 135.4, 132.8, 130.6, 130.3, 130.0, 127.9, 127.1, 126.2, 125.3, 119.19, 119.18, 118.4. Anal. Calcd for $C_{15}H_9BrClNO$: C, 53.84; H, 2.71. Found: C, 53.76; H, 2.72.

4-(2-Chlorophenyl)-7-fluoroquinolin-2(1*H*)-one (2r): yellow solid; mp 253−255 °C; IR (neat) 3399, 1594 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.04 (br s, 1 H), 7.65 (d, J = 7.6 Hz, 2 H), 7.57−7.44 (m, 3 H), 7.14 (d, J = 10.0, 1 H), 6.98 (d, J = 6.8, 2 H), 6.37 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 163.6 (d, J = 247.5 Hz), 161.9, 149.2, 140.9 (d, J = 12.4 Hz), 135.6, 132.0, 131.3, 131.2, 130.1, 129.0 (d, J = 10.5 Hz), 128.1, 121.6 (d, J = 2.3 Hz), 115.9 (d, J = 1.9 Hz), 110,7 (d, J = 23.4 Hz), 102.0 (d, J = 25.6 Hz); ^{19}F NMR (376.5 MHz) δ −108.8. Anal. Calcd for $C_{15}H_9ClFNO$: C, 65.83; H, 3.31. Found: C, 65.79; H, 3.32.

4-(2-Bromophenyl)-7-methylquinolin-2(1*H*)-one (2s): white solid; mp 228−231 °C; IR (KBr) 3440, 1564, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.81 (br s, 1 H), 7.75 (d, J = 7.6 Hz, 1 H), 7.49−7.46 (m, 1 H), 7.37−7.33 (m, 3 H), 7.026 (m, 2 H), 6.63 (s, 1 H), 2.48 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.3, 152.4, 141.8, 138.7, 138.2, 133.1, 130.6, 130.1, 127.5, 126.4, 124.4, 122.5, 120.4, 117.4, 116.4, 21.6. Anal. Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85. Found: C, 61.22; H, 3.84.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all the compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sandro.cacchi@uniroma1.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge MURST (FIRB 2008, Futuro in ricerca) and La Sapienza, University of Rome, for their financial support.

REFERENCES

(1) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
(2) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540.
(3) Sun, C. L.; Li, B. J.; Shi, Z. I. *Chem. Commun.* **2010**, *46*, 677.
(4) Zhang, M. *Appl. Organomet. Chem.* **2010**, *24*, 269.
(5) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641.
(6) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296.
(7) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072.
(8) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.
(9) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052.
(10) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078.
(11) Barbero, N.; SanMartin, R.; Domínguez, E. *Org. Biomol. Chem.* **2010**, *8*, 841.
(12) Liao, Q.; Zhang, L.; Li, S.; Xi, C. *Org. Lett.* **2011**, *13*, 228.
(13) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932.
(14) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.
(15) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607.
(16) He, H.-F.; Wang, Z.-J.; Bao, W. *Adv. Synth. Catal.* **2010**, *352*, 2905.
(17) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.
(18) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 1194.
(19) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522.
(20) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632.
(21) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.
(22) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411.
(23) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272.
(24) Freeman, G. A.; Andrews, , C. W. III; Hopkins, A. L.; Lowell, G. S.; Schaller, L. T.; Cowan, J. R.; Gonzales, S. S.; Koszalka, G. W.; Hazen, R. J.; Boone, L. R.; Rob, G.; Ferris, R. G.; Creech, K. L.; Roberts, G. B.; Short, S. A.; Weaver, K.; David, J.; Reynolds, D. J.; Milton, J.; Ren, J.; Stuart, D. I.; Stammers, D. K.; Chan, J. H. *J. Med. Chem.* **2004**, *47*, 5923.
(25) Wall, M. J.; Chen, J.; Meegalla, S.; Ballentine, S. K.; Wilson, K. J.; DesJarlais, R. L.; Schubert, C.; Chaikin, M. A.; Crysler, C.; Petrounia, I. P.; Donatelli, R. R.; Yurkow, E. J.; Boczon, L.; Mazzulla, M.; Player, M. R.; Patch, R. J.; Manthey, C. L.; Molloy, C.; Tomczuk, B.; Illig, C. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2097.
(26) Kraus, J. M.; Verlinde, C. L. M. J.; Karimi, M.; Lepesheva, G. I.; Gelb, M. H.; Buckner, F. S. *J. Med. Chem.* **2009**, *52*, 1639.
(27) See, for example: van Cutsem, E.; van de Velde, H.; Karasek, P.; Oettle, H.; Vervenne, W.; Szawlowski, L.; A.; Schoffski, P.; Post, S.; Verslype, C.; Neumann, H.; Safran, H.; Humblet, Y.; Ruixo, J. P.; Ma, Y.; von Hoff, D. *J. Clin. Oncol.* **2004**, *22*, 1430.
(28) See, for example: Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett* **1998**, 446.
(29) Larsen, R. D. *Sci. Synth.* **2005**, *15*, 551.
(30) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2006**, *128*, 722.
(31) Battistuzzi, G.; Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Adv. Svnth. Catal.* **2007**, *349*, 297.
(32) Tadd, A. C.; Malsuno, A.; Fieldim, M. R.; Willis, M. C. *Org. Lett.* **2009**, *11*, 583.
(33) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *J. Org. Chem.* **2010**, *75*, 3900.
(34) Bair, J. S.; Palchaudhuri, R.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 5469.
(35) Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Synlett* **2006**, 2947.
(36) Hay, L. A.; Koenig, T. M.; Ginah, F. O.; Copp, J. D.; Mitchell, D. *J. Org. Chem.* **1998**, *63*, 5050.
(37) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844.
(38) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727.
(39) Dieter, R. K.; Silks, , L. A. III; Fishpaugh, J. R.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679.
(40) Togunaka, M.; Shirogane, Y.; Aoyama, H.; Obara, Y.; Tsuji, Y. *J. Organomet. Chem.* **2005**, *690*, 5378.
(41) The notion that the effect of the ortho substituent on the aromatic ring *trans* to the amide group is basically steric in nature is based on the observation that the same trend is observed both with electron-donating (Table 2, entry 1) and with electron-withdrawing (Table 2, entries 2−7) substituents.
(42) One of the reviewers suggested another mechanistic possibility that involves the following basic steps: formation of copper(I) complexes (RCONH-Cu) as dimers or tetramers, coordination of O_2, formation of copper(II) or copper(III) intermediates, and attack of the arene on the NHCu (or deprotonated NCu) fragment.
(43) Calò, V.; Nacci, A.; Monopoli, A.; Ieva, E.; Cioffi, N. *Org. Lett.* **2005**, *7*, 617.
(44) Iyer, S.; Thakur, V. V. *J. Mol. Catal. A: Chem.* **2000**, *157*, 275.