JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

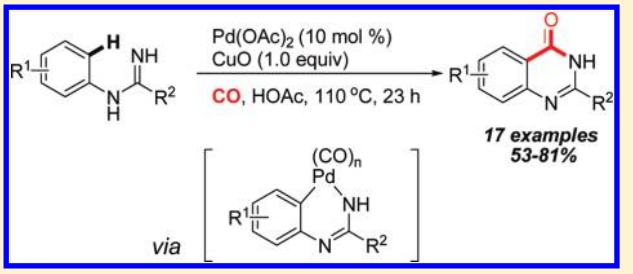
Synthesis of Quinazolin-4(3*H*)-ones via Pd(II)-Catalyzed Intramolecular C(sp^2)−H Carboxamidation of *N*-arylamidines

Bin Ma, Yong Wang, Jiangling Peng, and Qiang Zhu*

State Key Laboratory of Respiratory Disease, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 190 Kaiyuan Avenue, Guangzhou 510530, China

Supporting Information

ABSTRACT: An efficient synthesis of quinazolin-4(3*H*)-ones from *N*-arylamidines, through palladium-catalyzed intramolecular C(sp^2)−H carboxamidation, has been developed. The reaction, carried out in the presence of 1.0 equiv of CuO as oxidant under atmospheric pressure of CO, provides diversified 2-aryl(alkyl)-quinazolin-4(3*H*)-ones in reasonable to good yields from *N*-arylamidines, which are readily derived from anilines and nitriles. Compared with existing approaches to quinazolin-4(3*H*)-ones, the current strategy features atom-economy and step-efficiency.



Palladium-catalyzed carbonylation of alkenyl or aryl (pseudo)-halides represents a straightforward approach to carboxylic acids and their derivatives.[1] However, the requisite of using prefunctionalized (pseudo)halide substrates and the generation of environmentally unfriendly waste make alternative approaches highly desirable. Substantial achievements have been made in the area of direct functionalization of C−H bonds during the past decade.[2] Carbonylation of C−H bonds, catalyzed by transition metals under the aid of an appropriate directing group, has however attracted much less attention until very recently.[3,4] Compared with intermolecular C−H carbonylation,[3] the intramolecular fashion obviates the need for extra steps of introducing and removing the directing group which acts as an intramolecular nucleophile as well.[4] Therefore, the intramolecular C−H carbonylation is an ideal and truly atom-economical approach to lactones and lactams.[4] Herein, we would like to report a palladium-catalyzed intramolecular C(sp^2)−H carboxamidation of *N*-arylamidines, providing an efficient approach to diversified quinazolin-4(3*H*)-one derivatives.

Quinazolin-4(3*H*)-one is an important scaffold found in many natural products and synthetic drugs or drug candidates exhibiting a wide range of biological activities, including antibacterial,[5] antiinflammatory,[6] antifungal,[7] anticancer,[8] antimicrobial,[9] and antimalarial activities.[10] As a result, numerous synthetic efforts have been made for their synthesis.[11] The most widely used method is probably the condensation of 2-aminobenzoic acids or their derivatives with carboxylic acid derivatives under acidic or basic conditions (Scheme 1).[11,12] Recently, Fu developed novel cascade methods starting from 2-halobenzoic acids or 2-halobenzamides.[13] Alper and co-authors reported alternative approaches via tandem reactions involving palladium-catalyzed cyclocarbonylation of 2-iodoanilines or their derivatives as the key step.[14] We speculated that the quinazolin-4(3*H*)-one motif could also be constructed by palladium-catalyzed intramolecular C(sp^2)−H carboxamidation of simple *N*-arylamidines, which are derived readily from anilines and nitriles.[15] This strategy delivers quinazolin-4(3*H*)-ones in only two steps from commercial available chemicals, and no atoms except protons in substrates are lost during the process (Scheme 1).

The reaction conditions were optimized with *N*-phenylbenzamidine **1a** as substrate,[15,16] and the results are summarized in Table 1. Yu's conditions for the carboxylation of *o*-C−H bonds in anilides to form *N*-acylanthranilic acids, employing $Pd(OAc)_2$ (10 mol %), benzoquinone (BQ, 1.0 equiv), *p*-TsOH (0.5 equiv), HOAc/dioxane (2:1) as solvent, and atmospheric pressure of CO, were applied first (entry 1, Table 1).[3b] Gratifyingly, the desired product 2-phenylquinazolin-4(3*H*)-one **2a**, contaminated with small amount of hydroquinone, was formed in 34% yield (by NMR). To simplify the purification, inorganic oxidant $Cu(OAc)_2$ was used in place of BQ, and the yield of **2a** was improved from 52% to 59% in the absence of *p*-TsOH (entries 2−3, Table 1). Alteration of the palladium species to $PdCl_2$ or $Pd(TFA)_2$ did not improve the results. Other oxidants including $CuCl_2$, $PhI(OAc)_2$, AgOAc, $CuSO_4 \cdot 5H_2O$, and CuO were then screened (entries 6−10, Table 1), with CuO being the most effective. The selection of solvent was also crucial, identifying acetic acid as the optimum solvent (entries 11−13, Table 1).

With the optimized reaction conditions in hand, the scope of the palladium-catalyzed intramolecular C(sp^2)−H carboxamidation forming quinazolin-4(3*H*)-ones was investigated. As shown in Table 2, electron-donating groups on ortho-, meta-, and para-positions of the *N*-aryl moiety of **1** favored the reaction, providing corresponding substituted 2-phenylquinazolin-4(3*H*)-ones (**2b**−**g**) in reasonable to good yields. Notably, when two asymmetric C(sp^2)−H bonds were present in meta-substituted *N*-arylamidines **1e**,**f**, only the less hindered C−H bond was carbonylated. Unfortunately, substrates with electron-withdrawing

Received: April 8, 2011
Published: June 15, 2011

Scheme 1. Major Approaches to Quinazolin-4(3*H*)-ones

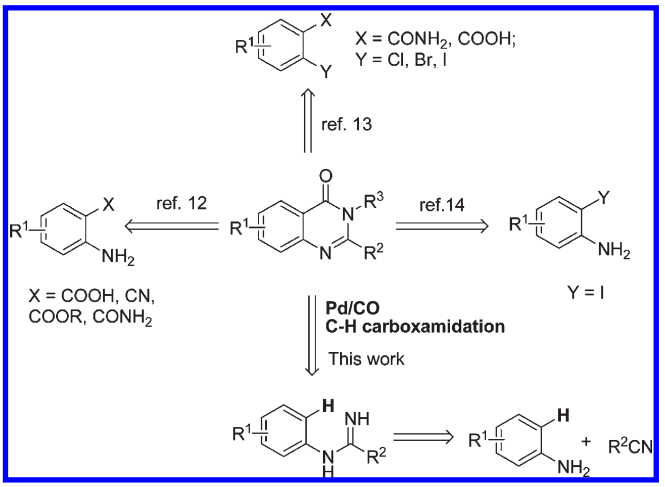
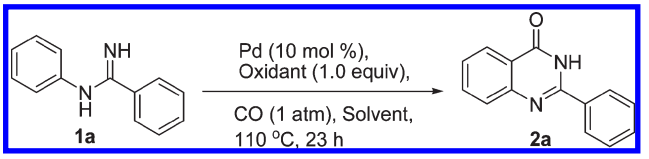


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (0.1 equiv)	oxidant (1.0 equiv)	solvent	yield (%)[b]
1[c]	$Pd(OAc)_2$	BQ	A[d]	34[e]
2[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	A	52
3	$Pd(OAc)_2$	$Cu(OAc)_2$	A	59
4	$PdCl_2$	$Cu(OAc)_2$	A	53
5	$Pd(TFA)_2$	$Cu(OAc)_2$	A	56
6	$Pd(OAc)_2$	$CuCl_2$	A	45
7	$Pd(OAc)_2$	$PhI(OAc)_2$	A	0
8	$Pd(OAc)_2$	AgOAc	A	27
9	$Pd(OAc)_2$	$CuSO_4 \cdot 5H_2O$	A	54
10	$Pd(OAc)_2$	CuO	A	61
11	$Pd(OAc)_2$	CuO	B[f]	23
12	$Pd(OAc)_2$	CuO	HOAc	69 (61)[g]
13	$Pd(OAc)_2$	CuO	TFA	trace

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (1.0 equiv), CO balloon (1 atm), solvent (1.5 mL), 110 °C, 23 h. [b] ^1H NMR yield. [c] 0.5 equiv of TsOH was added. [d] Solvent A: HOAc:dioxane (2:1). [e] Hydroquinone was detected in the product. [f] Solvent B: C_2H_5COOH:dioxane (2:1). [g] Isolated yield in parentheses.

groups, such as Cl and F, on any positions of the *N*-aryl ring were intact under the standard reaction conditions, suggesting that an electrophilic aromatic substitution (S_EAr) pathway may be involved in the C−H bond activation. Substitution effect on the benzamidine moiety was also examined. Electron-rich benzamidines (**1h**−**k**) provided much better results than electon-deficient ones, indicating that the electron density on the amidine nitrogen was crucial in chelation with the palladium catalyst. In general, less sterically hindered alkyl amidines were good substrates in the current C−H carboxamidation, yielding corresponding 2-alkylquinazolin-4(3*H*)-ones **2l**−**q** in up to 81% yield.

To gain insight into the reaction mechanism, monodeuterated *N*-phenylbenzamidine **1a-D** was subjected to the reaction conditions (Scheme 2). The reaction was quenched at 4 h, and the deuteration rates in both recovered starting material and the product were tested. It was found that the deuterium was partially lost in the recovered **1a-D** from over 95% to about 75%, and only one-third of the product was deuterium incorporated. The results suggested that the C−H bond activation was reversible and deuterium−hydrogen exchange occurred during the reaction.

Based on the results of substrate scope exploration and deuteration study, a plausible reaction mechanism is proposed in Scheme 3. Initial chelation of the amidine nitrogen with palladium(II) forms intermediate **A**, followed by reversible cyclopalladation. The coordinated CO inserts into the C−Pd bond in **B**, generating a seven-membered palladocycle **C**. Reductive elimination leads to the product **2** and releases Pd(0) which is reoxidized by CuO under the aid of HOAc.

In summary, we have developed an efficient synthesis of quinazolin-4(3*H*)-ones from *N*-arylamidines, through palladium-catalyzed intramolecular $C(sp^2)$−H carboxamidation. The reaction is carried out in the presence of $Pd(OAc)_2$ (10 mol %), and CuO (1.0 equiv), under 1 atm of CO atmosphere in HOAc, providing diversified 2-aryl(alkyl)quinazolin-4(3*H*)-ones in reasonable to good yields. The reaction proceeds smoothly with electron-rich *N*-arylamidines, which are readily derived from anilines and nitriles. Compared with existing approaches to quinazolin-4(3*H*)-ones, the current access features atom-economy and step-efficiency.

EXPERIMENTAL SECTION

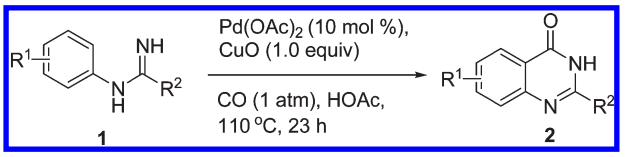
General Information. All reagents were purchased without further purification. Reactions were monitored using thin-layer chromatography (TLC) on commercial silica gel plates (GF254). Visualization of the developed plates was performed under UV light (254 nm). Flash column chromatography was performed on silica gel (200−300 mesh). ^1H and ^{13}C NMR spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts (δ) were reported in ppm referenced to an internal tetramethylsilane standard or the DMSO-d_6 residual peak (δ 2.50) for ^1H NMR. Chemical shifts of ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.0) or DMSO-d_6 (δ 39.5). High resolution mass spectra (HRMS) were obtained on an ESI-LC-MS/MS Spectrometer.

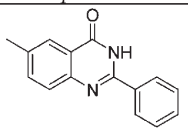
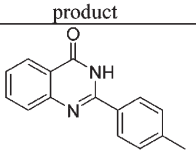
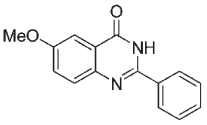
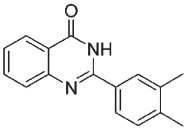
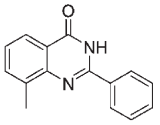
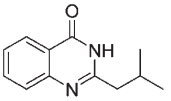
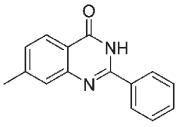
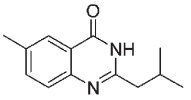
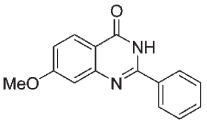
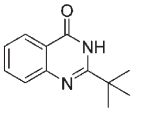
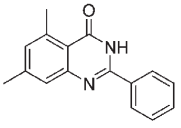
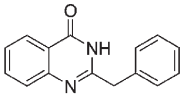
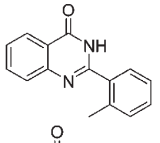
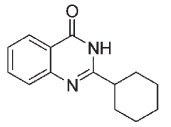
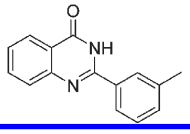
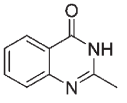
General Procedure for the Synthesis of Quinazolin-4(3*H*)-ones. A 10 mL Schlenk-type tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with substrate **1** (0.2 mmol), followed by $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), CuO (16 mg, 0.2 mmol), and acetic acid (1.5 mL) as solvent. The reaction tube was evacuated and back-filled with CO (five times, balloon) and heated to 110 °C for 23 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. The reaction mixture was neutralized with saturated solution of $NaHCO_3$ and then extracted with ethyl acetate. The aqueous layer was further extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Synthesis of *N*-(2-Deuteriophenyl)benzamidine 1a-D.[16,20] A dried round-bottom flask (25 mL in volume) was charged with NaH (60% in mineral oil) (180 mg, 4.5 mmol, 60%, 1.5 equiv). Under a stream of argon, DMSO (3 mL) was added, and the resulting suspension was cooled with an ice−water bath prior to the addition of 2-deuterioaniline (280 mg, 3 mmol, 1.0 equiv) and benzonitrile (0.33 mL, 3.3 mmol, 1.1 equiv). The mixture was kept at 0 °C for 60 min and then stirred

dx.doi.org/10.1021/jo2007362 |*J. Org. Chem.* 2011, 76, 6362–6366

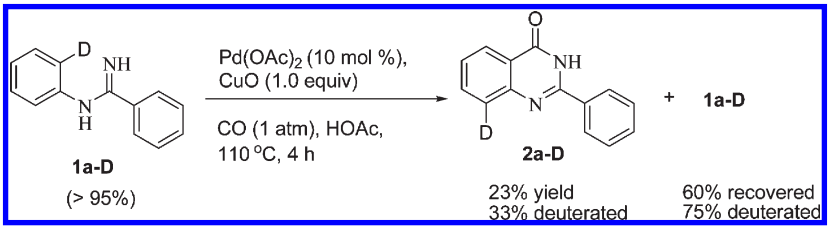
Table 2. Scope of Pd(II)-Catalyzed Intramolecular C(sp^2)−H Carboxamidation[a]



entry	1	product	2	yield (%)[b]	entry	1	product	2	yield (%)[b]
1	**1b** R^1 = 4-Me, R^2 = Ph		**2b**	68	9	**1j** R^1 = H, R^2 = 4-MeC_6H_4		**2j**	70
2	**1c** R^1 = 4-OMe, R^2 = Ph		**2c**	54	10	**1k** R^1 = H, R^2 = 3,4-di MeC_6H_3		**2k**	62
3	**1d** R^1 = 2-Me, R^2 = Ph		**2d**	53	11	**1l** R^1 = H, R^2 = *i*-Bu		**2l**	80
4	**1e** R^1 = 3-Me, R^2 = Ph		**2e**	72	12	**1m** R^1 = 4-Me, R^2 = *i*-Bu		**2m**	74
5	**1f** R^1 = 3-OMe, R^2 = Ph		**2f**	74	13	**1n** R^1 = H, R^2 = *t*-Bu		**2n**	60
6	**1g** R^1 = 3,5-diMe, R^2 = Ph		**2g**	70	14	**1o** R^1 = H, R^2 = Bn		**2o**	60
7	**1h** R^1 = H, R^2 = 2-MeC_6H_4		**2h**	74	15	**1p** R^1 = H, R^2 = cyclohexyl		**2p**	77
8	**1i** R^1 = H, R^2 = 3-MeC_6H_4		**2i**	53	16	**1q** R^1 = H, R^2 = Me		**2q**	81

[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), CuO (1.0 equiv), CO balloon (1 atm), HOAc (1.5 mL), 110 °C, 23 h. [b] Isolated yield of **2**.

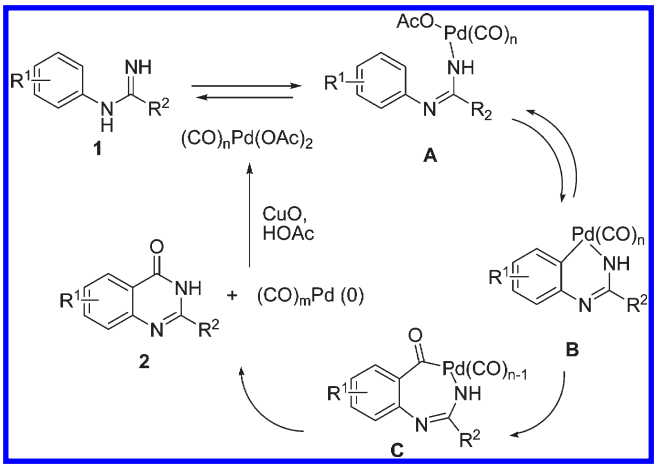
Scheme 2. Deuteration Study



at room temperature until the starting material was consumed as monitored by TLC analysis. Ice−water (10 mL) was added while maintaining vigorous stirring. The aqueous layer was extracted with EtOAc (3 × 10 mL). The extracts were combined and washed with water (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to get 414 mg (70%) of *N*-(2-deuteriophenyl)-benzamidine **1a-D**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 4.0 Hz,

dx.doi.org/10.1021/jo2007362 |*J. Org. Chem.* 2011, 76, 6362–6366

Scheme 3. Plausible Reaction Mechanism



2H), 7.46 (m, 3H), 7.36 (m, 2H), 7.07 (t, J = 7.2 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 4.85 (br, 2H).

Mechanistic Study. The reaction of *N*-(2-deuteriophenyl)benzamidine **1a-D** (20 mg, 0.1 mmol) was run for 4 h following the general procedure. The product was obtained in 5 mg (23%), and the starting material was recovered in 12 mg (60%). The deuteration rates of both product and recovered **1a-D** were determined by ^{1}H NMR integration (**2a**:**2a-D** = 2:1, **1a**:**1a-D** = 1: 3).

2-Phenylquinazolin-4(3*H*)-one (2a)[13c]**.** Eluent: petroleum ether/ethyl acetate (4:1). Yield: 61% (27 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (br, 1H), 8.17 (t, J = 7.2 Hz, 3H), 7.84 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.50−7.60 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.3, 152.4, 148.7, 134.6, 132.7, 131.4, 128.6, 127.8, 127.4, 126.6, 125.8, 121.0; Exact mass calcd for $C_{14}H_{11}N_2O$ [M + H]$^+$ 223.0866, Found 223.0875.

6-Methyl-2-phenylquinazolin-4(3*H*)-one (2b)[11d]**.** Eluent: petroleum ether/ethyl acetate (4:1). Yield: 68% (32 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (br, 1H), 8.16 (d, J = 6.4 Hz, 2H), 7.95 (s, 1H), 7.65 (s, 2H), 7.55 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.1, 151.4, 146.7, 136.3, 135.8, 132.7, 131.2, 128.5, 127.6, 127.3, 125.2, 120.7, 20.8; Exact mass calcd for $C_{15}H_{12}N_2NaO$ [M + Na]$^+$ 259.0842, Found 259.0834.

6-Methoxy-2-phenylquinazolin-4(3*H*)-one (2c)[13a]**.** Eluent: petroleum ether/ethyl acetate (4:1). Yield: 54% (27 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (br, 1H), 8.16 (d, J = 6.0 Hz, 2H), 7.70 (d, J = 8.8 Hz, 1 H), 7.55 (s, 4H), 7.45 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.0, 157.7, 150.1, 143.2, 132.8, 131.0, 129.2, 128.5, 127.5, 124.1, 121.8, 105.9, 55.6; Exact mass calcd for $C_{15}H_{13}N_2O_2$ [M + H]$^+$ 253.0972, Found 253.0984.

8-Methyl-2-phenylquinazolin-4(3*H*)-one (2d)[11d]**.** Eluent: petroleum ether/ethyl acetate (4:1). Yield: 53% (25 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (br, 1H), 8.22 (d, J = 6.8 Hz, 2H), 8.00 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 6.8 Hz, 1H), 7.56 (m, 3H), 7.38 (t, J = 7.6 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.5, 151.0, 147.1, 135.6, 134.9, 132.9, 131.3, 128.6, 127.7, 126.1, 123.5, 120.9, 17.1; Exact mass calcd for $C_{15}H_{13}N_2O$ [M + H]$^+$ 237.1022, Found 237.1018.

7-Methyl-2-phenylquinazolin-4(3*H*)-one (2e)[13a]**.** Eluent: petroleum ether/ethyl acetate (4:1). Yield: 72% (34 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (br, 1H), 8.16 (d, J = 6.8 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1 H), 7.56 (m, 4H), 7.33 (d, J = 8.0 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.1, 152.3, 148.8, 145.0, 132.8, 131.3, 128.6, 128.0, 127.7, 127.1, 125.7, 118.6, 21.3; Exact mass calcd for $C_{15}H_{13}N_2O$ [M + H]$^+$ 237.1022, Found 237.1008.

7-Methoxy-2-phenylquinazolin-4(3*H*)-one (2f)[11e]**.** Eluent: petroleum ether/ethyl acetate (4:1). Yield: 74% (39 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (br, 1H), 8.17 (d, J = 7.2 Hz, 2H), 8.05 (d, J = 8.8 Hz, 1H), 7.56 (m, 3H), 7.19 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.2, 161.7, 152.9, 151.0, 132.7, 131.4, 128.5, 127.7, 127.4, 116.2, 114.4, 108.5, 55.7; Exact mass calcd for $C_{15}H_{13}N_2O_2$ [M + H]$^+$ 253.0972, Found 253.0985.

5,7-Dimethyl-2-phenylquinazolin-4(3*H*)-one (2g)[17]**.** Eluent: petroleum ether/ethyl acetate (4:1). Yield: 70% (35 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (br, 1H), 8.16 (d, J = 7.2 Hz, 2H), 7.56 (m, 3H), 7.37 (s, 1H), 7.09 (s, 1H), 2.77 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.8, 151.9, 150.4, 143.8, 139.6, 132.5, 131.2, 130.3, 128.5, 127.6, 125.4, 116.9, 22.3, 21.0; Exact mass calcd for $C_{16}H_{15}N_2O$ [M + H]$^+$ 251.1179, Found 251.1152.

2-*o*-Tolylquinazolin-4(3*H*)-one (2h)[18]**.** Eluent: petroleum ether/ethyl acetate (6:1). Yield: 74% (35 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (br, 1H), 8.16 (d, J = 7.2 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 6.4 Hz, 1H), 7.35 (d, J = 4.8 Hz, 1H), 7.32 (t, J = 5.2 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.8, 154.4, 148.7, 136.1, 134.4, 134.2, 130.5, 129.8, 129.1, 127.3, 126.6, 125.7, 125.6, 120.9, 19.5; Exact mass calcd for $C_{15}H_{13}N_2O$ [M + H]$^+$ 237.1022, Found 237.0996.

2-*m*-Tolylquinazolin-4(3*H*)-one (2i)[11e]**.** Eluent: petroleum ether/ethyl acetate (4:1). Yield: 53% (25 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (br, 1H), 8.15 (d, J = 7.6 Hz, 1H), 8.03 (s, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.43 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2, 152.3, 148.7, 137.9, 134.6, 132.6, 132.0, 128.5, 128.2, 127.4, 126.5, 125.8, 124.9, 121.0, 20.9; Exact mass calcd for $C_{15}H_{13}N_2O$ [M + H]$^+$ 237.1022, Found 237.1001.

2-*p*-Tolylquinazolin-4(3*H*)-one (2j)[13a]**.** Eluent: petroleum ether/ethyl acetate (4:1). Yield: 70% (33 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (br, 1H), 8.14 (d, J = 8 Hz, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.82 (t, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.52 (t, J = 8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2, 152.2, 148.8, 141.4, 129.9, 129.1, 127.6, 127.4, 126.3, 125.8, 120.9, 20.9; Exact mass calcd for $C_{15}H_{12}N_2NaO$ [M + Na]$^+$ 259.0842, Found 259.0828.

2-(3,4-Dimethylphenyl)quinazolin-4(3*H*)-one (2k). Eluent: petroleum ether/ethyl acetate (4:1). Yield: 62% (31 mg). White solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.40 (br, 1H), 8.14 (d, J = 8 Hz, 1H), 8.01 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.81 (t, J = 7.5, 1H), 7.73 (d, J = 8 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 8 Hz, 1 H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2, 152.3, 148.8, 140.2, 136.5, 134.5, 130.1, 129.6, 128.6, 127.4, 126.3, 125.8, 125.1, 120.9, 19.4, 19.3; Exact mass calcd for $C_{16}H_{15}N_2O$ [M + H]$^+$ 251.1179, Found 251.1151.

2-Isobutylquinazolin-4(3*H*)-one (2l)[13e]**.** Eluent: petroleum ether/ethyl acetate (6:1). Yield: 80% (32 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (br, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 2.47 (d, J = 7.2 Hz, 2H), 2.18 (m, 1H), 0.92 (d, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.8, 156.7, 148.9, 134.2, 126.8, 125.9, 125.6, 120.7, 43.3, 27.0, 22.1; Exact mass calcd for $C_{12}H_{15}N_2O$ [M + H]$^+$ 203.1179, Found 203.1195.

2-Isobutyl-7-methylquinazolin-4(3*H*)-one (2m)[13e]**.** Eluent: petroleum ether/ethyl acetate (6:1). Yield: 74% (32 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (br, 1H), 7.87 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 2.45 (d, J = 7.2 Hz, 2H), 2.42 (s, 3H), 2.18 (m, 1H), 0.92 (d, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7, 155.8, 146.9, 135.5, 135.4, 126.7, 125.0, 120.5, 43.2, 27.0, 22.1, 20.7; Exact mass calcd for $C_{13}H_{17}N_2O$ [M + H]$^+$ 217.1335, Found 217.1332.

dx.doi.org/10.1021/jo2007362 |*J. Org. Chem.* 2011, 76, 6362–6366

2-*tert*-Butylquinazolin-4(3*H*)-one (2n)[11d]**.** Eluent: petroleum ether/ethyl acetate (6:1). Yield: 60% (24 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (br, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.6, 162.3, 148.3, 134.3, 127.3, 126.2, 125.6, 120.6, 37.2, 27.8; Exact mass calcd for $C_{12}H_{15}N_2O$ $[M + H]^+$ 203.1179, Found 203.1185.

2-Benzylquinazolin-4(3*H*)-one (2o)[19]**.** Eluent: petroleum ether/ethyl acetate (7:1). Yield: 60% (28 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (br, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.77 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.8 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 3.93 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.8, 155.9, 148.9, 136.5, 134.4, 128.8, 128.5, 126.9, 126.8, 126.2, 125.7, 120.7, 40.7; Exact mass calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$ 237.1022, Found 237.1017.

2-Cyclohexylquinazolin-4(3*H*)-one (2p)[12d]**.** Eluent: petroleum ether/ethyl acetate (6:1). Yield: 77% (35 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 2.57 (m, 1H), 1.90 (m, 2H), 1.79 (m, 2H), 1.68 (m, 1H), 1.58 (m, 2H), 1.28 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.9, 160.7, 148.9, 134.2, 126.9, 125.8, 125.6, 120.9, 42.8, 30.2, 25.5, 25.3; Exact mass calcd for $C_{14}H_{17}N_2O$ $[M + H]^+$ 229.1335, Found 229.1338.

2-Methylquinazolin-4(3*H*)-one (2q)[13c]**.** Eluent: petroleum ether/ethyl acetate (6:1). Yield: 81% (26 mg). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (br, 1H), 8.07 (d, J = 6.4 Hz, 1H), 7.76 (t, J = 6.0 Hz, 1H), 7.56 (d, J = 6.4 Hz, 1H), 7.45 (t, J = 6.0 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7, 154.2, 148.9, 134.2, 126.5, 125.8, 125.6, 120.6, 21.4; Exact mass calcd for $C_9H_9N_2O$ $[M + H]^+$ 161.0709, Found 161.0725.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ^{1}H and ^{13}C NMR spectra of all the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhu_qiang@gibh.ac.cn.

■ ACKNOWLEDGMENT

We are grateful to the National Science Foundation of China (21072190) and National Basic Research Program of China (973 Program 2011CB504004 and 2010CB945500) for financial support of this work.

■ REFERENCES

(1) (a) Skoda-Foldes, R.; Kollar, L. *Curr. Org. Chem.* **2002**, *6*, 1097. (b) Colquhoun, H. M., Thompson, D. J., Twigg, M. V. *Carbonylation, Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991.

(2) For selected recent reviews on transition metal-catalyzed C−H functionalization, see: (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (e) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (f) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(3) For examples of intermolecular C−H carbonylation, see: (a) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (b) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686. (c) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830.

(4) For examples of intramolecular C−H carbonylation, see: (a) Haffemayer, B.; Gulias, M.; Gaunt., M. J. *Chem. Sci.* **2011**, *2*, 312. (b) Yoo, E.-J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (c) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (d) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* **2011**, *2*, 967.

(5) Kung, P. P.; Casper, M. D.; Cook, K. L.; Wilson-Lingard, L.; Risen, L. M.; Vickers, T. A.; Ranken, R.; Blyn, L. B.; Wyatt, R.; Cook, P. D.; Ecker, D. J. *J. Med. Chem.* **1999**, *42*, 4705.

(6) (a) Lowe, J. A.; Archer, R. L.; Chapin, D. S.; Cheng, J. B.; Helweg, D.; Johnson, J. L.; Koe, B. K.; Lebel, L. A.; Moore, P. F.; Nielsen, J. A.; Russo, L. L.; Shirley, J. T. *J. Med. Chem.* **1991**, *34*, 624. (b) de Laszlo, S. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Chen, T.-B.; Scheck, S. A.; Faust, K. A.; Kivlighn, S. S.; Schorn, T. S.; Zingaro, G. J.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 3207.

(7) Liverton, N. J.; Armstrong, D. J.; Claremon, D. A.; Remy, D. C.; Baldwin, J. J.; Lynch, R. J.; Zhang, G.; Gould, R. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 483.

(8) (a) Jiang, J. B.; Hesson, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. *J. Med. Chem.* **1990**, *33*, 1721. (b) Cao, S. L.; Feng, Y. P.; Jiang, Y. Y.; Liu, S. Y.; Ding, G. Y.; Li, R. T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1915.

(9) (a) Habib, O. M.; Moawad, E. B.; Girges, M. M.; El-Shafei, A. M. *Boll. Chim. Farm.* **1995**, *134*, 503. (b) Ibrahim, S. S.; Abdel-Halim, A. M.; Gabr, Y.; El-Edfawy, S.; Abdel-Rahman, R. *J. Chem. Res., Synop.* **1997**, 154.

(10) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175.

(11) (a) Eguchi, S. *Heterocyl. Chem.* **2006**, *6*, 113. (b) Connolly, D, J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153. (c) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659. (d) Zhang, X. D.; Ye, D. J.; Sun, H. F.; Guo, D. L.; Wang, J.; Huang, H.; Zhang, X.; Jiang, H. L.; Liu, H. *Green Chem.* **2009**, *11*, 1881. (e) Gupta, S.; Agarwal, P. K.; Kundu, K. B. *Tetrahedron Lett.* **2010**, *51*, 1887.

(12) (a) Wu, H.; Xie, X.; Liu, G. *J. Comb. Chem.* **2010**, *12*, 346. (b) Feng, E.; Zhou, Y.; Zhang, D.; Zhang, L.; Sun, H.; Jiang, H.; Liu, H. *J. Org. Chem.* **2010**, *75*, 3274. (c) Dabiri, M.; Baghbanzadeh, M.; Delbari, A. S. *J. Comb. Chem.* **2008**, *10*, 700. (d) Connolly, D. J.; Guiry, P. J. *Synlett.* **2001**, *11*, 1707.

(13) (a) Xu, W.; Jin, Y.; Liu, H.; Jiang, H.; Fu, H. *Org. Lett.* **2011**, *13*, 1274. (b) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. *J. Comb. Chem.* **2009**, *11*, 653. (c) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 348. (d) Huang, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Commun.* **2008**, *47*, 6333. (e) Xu, W.; Fu, H. *J. Org. Chem.* **2011**, *76*, 3846.

(14) (a) Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 3642. (b) Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 1188. (c) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 829.

(15) (a) Singh, B.; Collins, J. C. *Chem. Commun.* **1971**, 498. (b) Ogonor, J. I. *Tetrahedron* **1981**, *37*, 2909.

(16) (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (b) Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. *Chem.—Eur. J.* **2009**, *15*, 7292.

(17) Ried, W.; Valentin., J. *Liebigs Ann.* **1967**, *707*, 250.

(18) Potewar, T. M.; Nadaf, R. N.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Synth. Commun.* **2005**, *35*, 231.

(19) Adib, M.; Ansari, S.; Mohammadi, A.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2010**, *51*, 32.

(20) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217.