Copper(I) Iodide Catalyzed Synthesis of Quinolinones via Cascade Reactions of 2-Halobenzocarbonyls with 2-Arylacetamides

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Abstract: An efficient copper-catalyzed method for the synthesis of quinolinones, pyridinones, and heteroannulated pyridinones via cascade reactions of substituted 2-iodo-, 2-bromo-, and 2-chlorobenzocarbonyls with 2-arylacetamides is reported. The protocol works well for the reaction of most of the 2-iodo-, 2-bromo- and 2-chlorobenzocarbonyls with 2-arylacetamides.

Key words: copper iodide, diamines, cascade reactions, amidation, quinolinones

Quinolinones, pyridinones, and heteroannulated pyridinones, represent an important class of motifs in natural products[2] and biologically active compounds[3] as well as valuable intermediates in organic synthesis.[4] The synthesis of this class of compounds has attracted huge efforts and a number of methods have been discovered, such as Knorr synthesis, cyclization/rearrangement, tandem Ugi–Knoevenagel condensations, intramolecular Friedel–Crafts reaction of *N*-arylamides, and microwave-assisted methods.[5] In recent years, palladium-catalyzed coupling reactions have been utilized in the construction of these kinds of compounds with great success.[5,6] Copper-catalyzed synthesis of these compounds was also reported with limited success.[5a] In continuation of our interest in copper-catalyzed coupling reactions[7] and to meet our need of quinolinones, pyridinones, and heteroannulated pyridinones for random biological screening, we report here an economic and efficient diamine-promoted copper-catalyzed process for this class of compounds via cascade amidation/dehydrative cyclization reactions of substituted 2-iodo-, 2-bromo-, and 2-chlorobenzocarbonyls with 2-arylacetamides.

The investigation was initiated by the coupling of 2-bromoacetophenone with 2-phenylacetamide as the model reaction (Table 1). Although no desired product was detected in the absence of copper salts, we were pleased to find that the 4-methyl-3-phenylquinolin-2(1*H*)-one product (**1**) was obtained in 24% yield under the catalysis of 10 mol% copper(I) iodide at 110 °C using cesium carbonate as the necessary base in toluene (Table 1, entries 1 and 2), indicating that copper catalyst was essential for this cascade reaction. Further investigation revealed that the well-known supporting ligands such as L-proline, 1,10-phenanthroline, or diamine compounds such as *N*,*N*′-dimethylethylenediamine (DMEDA), cyclohexane-1,2-diamine, ethylenediamine (EDA), (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine, and benzene-1,2-diamine could significantly improve the reaction efficiency (Table 1, entries 3–9). When 10 mol% of ethylenediamine was utilized, about 90% of the desired product was isolated after the reaction was performed at 110 °C for 24 hours (Table 1, entry 7). Further screening conditions suggested that other common inorganic bases such as potassium carbonate or potassium phosphate was also efficient for the cascade reactions (Table 1, entries 10 and 11). Investigation on the reaction medium revealed that toluene was the optimal solvent for this new reaction, while polar solvent *N*,*N*-dimethylformamide was highly detrimental (Table 1, entry 13). The combination of 10% copper(I) iodide, 20% ethylenediamine, and 300% cesium carbonate in toluene at 110 °C was chosen as the optimal condition for further investigations.

Under the optimized conditions, the scope of this new protocol was further explored by using the combinations of 2-phenylacetamide with a variety of 2-halobenzocarbonyls. As shown in Table 2, most of the substrates examined afforded the desired products in good to excellent yields. Aryl iodides exhibited superior reactivity than the aryl bromide substrates (Table 2, entries 1 and 10). When *o*-halo aldehydes served as the substrates, the shift of supporting ligand from ethylenediamine to DMEDA is necessary to ensure the efficiency of the catalyst system (Table 2, entries 9–17). (*Z*)-4-Bromo-3,4-diphenylbut-3-en-2-one and (*Z*)-3-bromo-2,3-diphenylacrylaldehyde could also react with 2-phenylacetamide to afford the corresponding pyridinones (Table 2, entries 8 and 9). It was noteworthy that the method also worked well for heteroaromatic bromide substrates (Table 2, entries 6, 7, 16, and 17). Moreover, the equivalents of carbonyl functional group were also effective in the cascade reactions (Table 2, entries 18 and 19).

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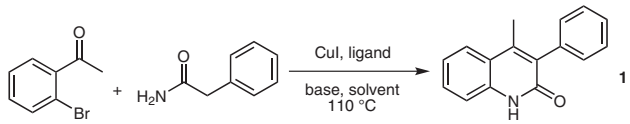
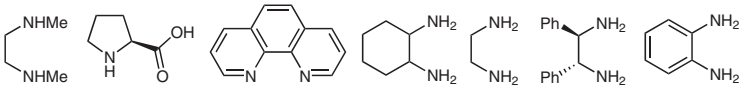
Table 1 Optimization of Copper-Catalyzed Cascade Reactions of 2-Bromoacetophenone with 2-Phenylacetamide[a]





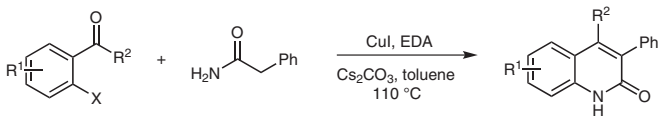
Entry	Ligand	Base	Solvent	Yield (%)[b]
1	–	Cs_2CO_3	toluene	trace[c]
2	–	Cs_2CO_3	toluene	24[d]
3	**A**	Cs_2CO_3	toluene	82
4	**B**	Cs_2CO_3	toluene	55
5	**C**	Cs_2CO_3	toluene	33
6	**D**	Cs_2CO_3	toluene	63
7	**E**	Cs_2CO_3	toluene	91
8	**F**	Cs_2CO_3	toluene	51
9	**G**	Cs_2CO_3	toluene	42
10	**E**	K_2CO_3	toluene	42
11	**E**	K_3PO_4	toluene	61
12	**E**	Cs_2CO_3	1,4-dioxane	52
13	**E**	Cs_2CO_3	DMF	35
14	**E**	Cs_2CO_3	dimethylglycol	46

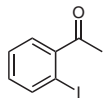
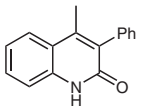
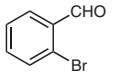
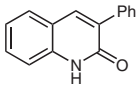
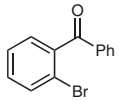
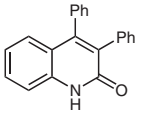
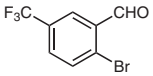
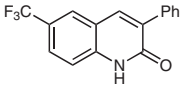
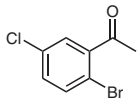
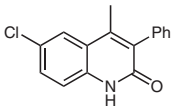
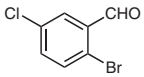
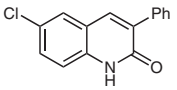
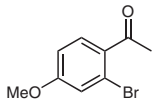
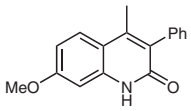
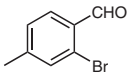
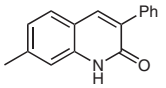
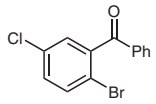
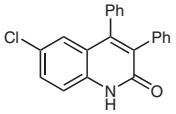
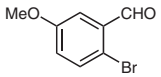
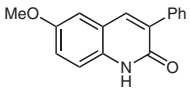
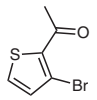
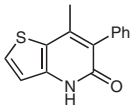
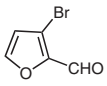
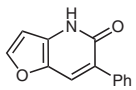
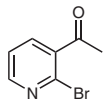
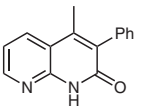
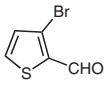
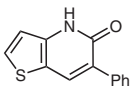
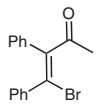
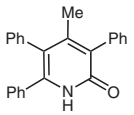
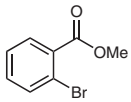
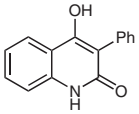
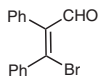
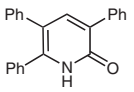
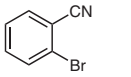
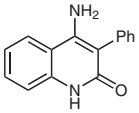
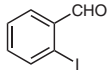
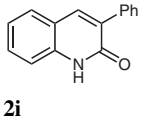
[a] Reaction conditions: 2-bromoacetophenone (1.0 mmol), 2-phenylacetamide (1.2 mmol), CuI (0.1 mmol), ligand (0.2 mmol), base (3.0 mmol), solvent (1.5 mL), argon atmosphere, 110 °C, 24 h.
[b] Isolated yield.
[c] No CuI nor ligand.
[d] No ligand.

The scope of the amide coupling partner was also explored. As shown in Table 3, most of the results were satisfactory. It was also demonstrated that the electronic density of the amide might have some impact on the efficiency of reaction, since electron-withdrawing group on the aromatic ring of the amide significantly reduced the yields (Table 3, entries 1–3). In addition, heterocyclic acetamides, such as 2-(1-methyl-1*H*-indol-3-yl)acetamide, 3-pyridylacetamide, and 2-pyridylacetamide also reacted smoothly to offer the desired products (Table 3, entries 4–6). Though the secondary amide, *N*-cyclopropyl-2-phenylactamide, afforded the product in low yield (Table 3, entry 7), *N*-phenyl-2-phenylacetamide worked well in the reaction (Table 3, entry 8). Unfortunately, this method did not work well for alkylacetamides (Table 3, entries 9 and 10).

The protocol also worked for aryl chlorides, the highly challenging substrates in most copper-catalyzed coupling reactions. Though the target product was obtained in 21% yield when 2-chloroacetophenone was coupled with 2-phenylacetamide at 110 °C, the yield increased to 42% when the reaction was performed at 150 °C (Table 4, entry 1). The reaction also worked well for several other substituted 2-chlorobenzocarbonyls to afford the desired products in moderate yields (Table 4, entries 2–8).

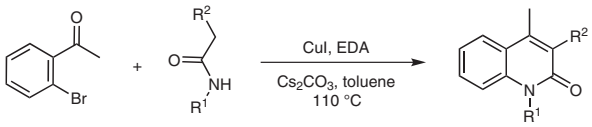
Table 2 Copper-Catalyzed Synthesis of Quinolinones, Pyridinones, and Heteroannulated Pyridinones: Investigation on the Scope of the Carbonyl Functional Group[a]

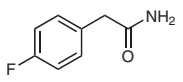
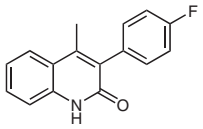
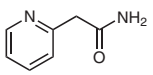
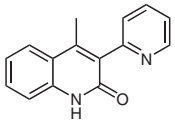
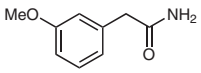
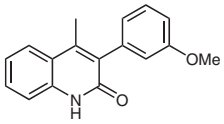
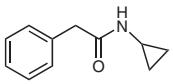
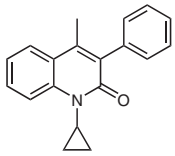
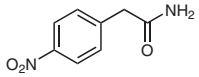
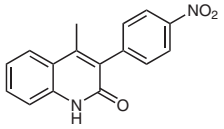
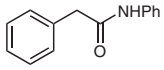
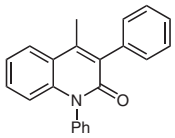
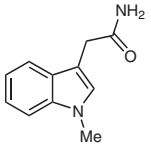
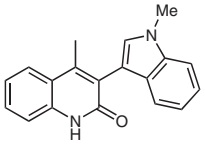
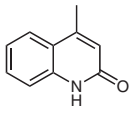
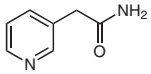
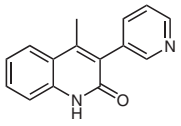
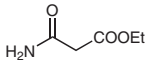
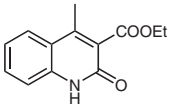


Entry	Aryl halide	Product	Yield (%)[b]	Entry	ArX	Product	Yield (%)[b]
1		 **1**	93	11		 **2i**	73[c]
2		 **2a**	93	12		 **2j**	62[c]
3		 **2b**	75	13		 **2k**	51[c]
4		 **2c**	77	14		 **2l**	58[c]
5		 **2d**	78	15		 **2m**	51[c]
6		 **2e**	74	16		 **2n**	61[c]
7		 **2f**	34	17		 **2o**	67[c]
8		 **2g**	31	18		 **2p**	46
9		 **2h**	50[c]	19		 **2q**	76
10		 **2i**	81[c]				

[a] Reaction conditions: ArX (1.0 mmol), 2-phenylacetamide (1.2 mmol), CuI (0.1 mmol), EDA (0.2 mmol), Cs_2CO_3 (3.0 mmol), toluene (1.5 mL), argon, 110 °C, 24 h.
[b] Isolated yield.
[c] DMEDA was used as the ligand.

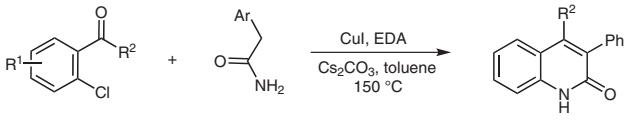
Table 3 Copper-Catalyzed Synthesis of Quinolinones, Pyridinones, and Heteroannulated Pyridinones: Investigation on the Scope of the Amide Coupling Partner[a]



Entry	Amide	Product	Yield (%)[b]	Entry	Amide	Product	Yield (%)[b]
1		 **3a**	85	6		 **3f**	65
2		 **3b**	80	7		 **3g**	20
3		 **3c**	20	8		 **3h**	64
4		 **3d**	62	9			trace
5		 **3e**	71	10			trace

[a] Reaction conditions: 2-bromoacetophenone (1.0 mmol), amide (1.2 mmol), CuI (0.1 mmol), EDA (0.2 mmol), Cs_2CO_3 (3.0 mmol), toluene (1.5 mL), argon, 110 °C, 24 h.
[b] Isolated yield.

Table 4 Copper-Catalyzed Cascade Reactions of 2-Phenylacetamides with 2-Chlorobenzocarbonyl Compounds[a]



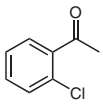
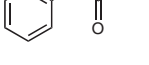
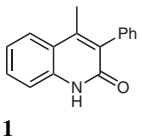
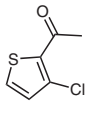
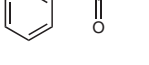
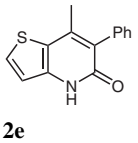
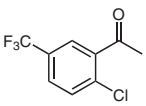
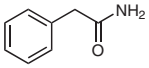
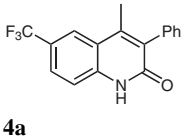
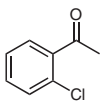
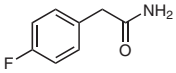
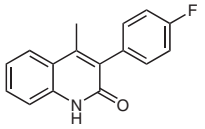
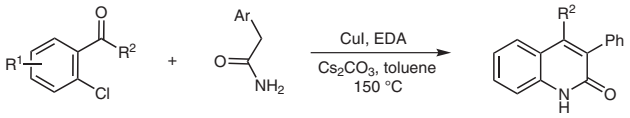
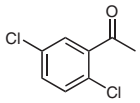
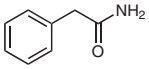
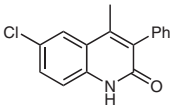
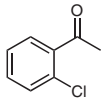
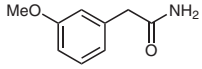
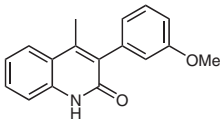
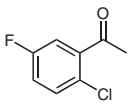
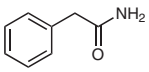
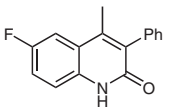
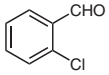
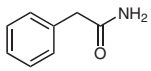
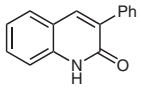
Entry	ArCl	Amide	Product	Yield (%)[b]	Entry	ArCl	Amide	Product	Yield (%)[b]
1			 **1**	42 21[c]	5			 **2e**	41
2			 **4a**	40	6			 **3a**	41

Table 4 Copper-Catalyzed Cascade Reactions of 2-Phenylacetamides with 2-Chlorobenzocarbonyl Compounds[a] (continued)



Entry	ArCl	Amide	Product	Yield (%)[b]	Entry	ArCl	Amide	Product	Yield (%)[b]
3			 **2b**	37	7			 **3b**	37
4			 **4b**	35	8			 **2i**	40[d]

[a] Reaction conditions: ArCl (1.0 mmol), amide (1.2 mmol), CuI (0.1 mmol), EDA (0.2 mmol), Cs_2CO_3 (3.0 mmol), toluene (1.5 mL), argon, 150 °C, 24 h.
[b] Isolated yield.
[c] 110 °C.
[d] DMEDA was used as the ligand.

All reactions were carried out in 10 mL sealed tubes, under a pure and dry argon atmosphere. Toluene was distilled from Na and was stored on 4Å activated molecular sieves. Cs_2CO_3 (Alfa Aesar), K_3PO_4 (Alfa Aesar), K_2CO_3, 2-phenylacetamide, CuI (Aldrich), and all other solid materials were stored in the presence of P_2O_5 in a bench-top desiccator under vacuum at r.t. and weighed in the air. 2-Halobenzocarbonyls and 2-phenylactamide amides were purchased from commercial sources (Aldrich, Acros, 3B, Alfa Aesar) and in most cases used directly without further purification or prepared according to literature. Column chromatography was performed with QDHY 60 A C.C. silica gel (35–70 mm). All products were characterized by NMR, LC/MS, or HRMS. NMR spectra were recorded at 20 °C on a Bruker AC 400 MHz spectrometer working, respectively, at 400 MHz for ^{1}H, at 500 MHz for ^{13}C. Chemical shifts are reported in ppm relative to solvent ($CDCl_3$: 7.27 and 77.0 ppm; DMSO-d_6: 2.50 and 39.51 ppm in ^{1}H and ^{13}C NMR spectra, respectively). The first order peak patterns are indicated as s (singlet), d (doublet), t (triplet), q (quadruplet). Complex non-first-order signals are indicated as m (multiplet). Low- and high-resolution ESI-MS were recorded on an Agilent 1200 HPLC-MSD mass spectrometer and an Applied Biosystems Q-STAR Elite ESI-LC-MS/MS mass spectrometer, respectively. Melting points were measured on an OptiMelt MPA 100 melting point apparatus and are uncorrected. Chemical names were generated using CambridgeSoft ChemDraw Ultra 10.0.

Compounds 1–4; General Procedure

A sealed tube was charged with a magnetic stir bar, 2-halobenzocarbonyl compound (1.0 mmol, if solid), 2-arylacetamide (1.2 mmol), CuI (5–10 mmol%), and Cs_2CO_3 (977.4 mg, 3.0 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). The 2-halobenzocarbonyl compound (1.0 mmol, if liquid), toluene (1.5 mL), and ligand (20 mmol%) were added by syringe under a counter-flow of argon. The tube was evacuated and backfilled with argon (this procedure was repeated three times) and sealed. Then the reaction mixture was heated to the indicated temperature for 24 h. After cooling to r.t., the mixture was diluted with CH_2Cl_2 (10 mL) and MeOH (5 mL), passed through a fritted glass filter, and then concentrated under vacuum (this procedure was repeated three times). Purification of the residue by column chromatography on silica gel (eluent: CH_2Cl_2–EtOAc, 4:1) afforded the desired product.

4-Methyl-3-phenylquinolin-2(1*H*)-one (1)[6a,b]

Light yellow solid; mp 264–266 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.55 (br s, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.39–7.51 (m, 4 H), 7.35 (d, *J* = 7.6 Hz, 2 H), 7.21–7.27 (m, 2 H), 2.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.0, 144.7, 137.4, 136.0, 132.3, 130.3, 130.0, 128.2, 127.5, 124.9, 122.3, 120.9, 116.1, 16.9.

ESI-MS: *m*/*z* = 236 (M + 1).

3, 4-Diphenylquinolin-2(1*H*)-one (2a)[6a,b]

White solid; mp 307–309 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.87 (br s, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.17–7.35 (m, 10 H), 7.06–7.14 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 149.8, 137.9, 136.3, 135.2, 131.9, 130.9, 130.2, 129.8, 128.0, 127.6, 127.5, 127.5, 127.0, 122.3, 120.9, 115.9.

ESI-MS: *m*/*z* = 298 (M + 1).

6-Chloro-4-methyl-3-phenylquinolin-2(1*H*)-one (2b)

White solid; mp 272–274 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.89 (br s, 1 H), 7.69 (d, *J* = 2.0 Hz, 1 H), 7.41–7.51 (m, 3 H), 7.32–7.38 (m, 3 H), 7.17 (d, *J* = 8.8 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.9, 143.8, 135.9, 135.6, 133.2, 130.2, 130.2, 128.3, 127.8, 127.7, 124.4, 122.0, 117.6, 16.9.

HRMS: *m*/*z* calcd for $C_{16}H_{13}ClNO$: 270.0680 $[M + H]^+$; found: 270.0681.

7-Methoxy-4-methyl-3-phenylquinolin-2(1*H*)-one (2c)

White solid; mp 241–243 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.26 (br s, 1 H), 7.63 (d, *J* = 9.2 Hz, 1 H), 7.43–7.47 (m, 2 H), 7.32–7.39 (m, 3 H), 6.83 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.71 (d, *J* = 2.4 Hz, 1 H), 3.83 (s, 3 H), 2.32 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 161.3, 144.8, 139.1, 136.2, 130.5, 129.4, 128.1, 127.4, 126.4, 115.0, 111.9, 98.1, 55.5, 16.9.

HRMS: *m*/*z* calcd for $C_{17}H_{16}NO_2$: 266.1176 $[M + H]^+$; found: 266.1173.

6-Chloro-3,4-diphenylquinolin-2(1*H*)-one (2d)[8a]
White solid; mp 303–305 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.96 (br s, 1 H), 7.37 (dd, *J* = 9.2, 2.4 Hz, 1 H), 7.29–7.31 (m, 3 H), 7.10–7.24 (m, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 148.9, 136.4, 135.6, 134.9, 132.9, 130.7, 130.5, 129.7, 128.2, 128.0, 127.7, 127.6, 127.2, 126.6, 121.9, 117.5.

HRMS: *m*/*z* calcd for $C_{21}H_{15}ClNO$: 332.0837 $[M + H]^+$; found: 332.0840.

7-Methyl-6-phenylthieno[3,2-*b*]pyridin-5(4*H*)-one (2e)
White solid; mp 234–236.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.27 (br s, 1 H), 7.45–7.49 (m, 2 H), 7.34–7.41 (m, 4 H), 6.95 (d, *J* = 5.6 Hz, 1 H), 2.28 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.8, 142.7, 140.2, 135.8, 130.5, 128.5, 128.2, 127.6, 127.4, 121.6, 117.9, 19.1.

HRMS: *m*/*z* calcd for $C_{14}H_{12}NOS$: 242.0634 $[M + H]^+$; found: 242.0636.

4-Methyl-3-phenyl-1,8-naphthyridin-2(1*H*)-one (2f)
White solid; mp 296–298 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.82 (br s, 1 H), 8.75 (d, *J* = 2.8 Hz, 1 H), 8.08 (d, *J* = 7.6 Hz, 1 H), 7.40–7.48 (m, 3 H), 7.24–7.33 (m, 3 H), 2.35 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6, 149.8, 148.8, 142.8, 135.2, 133.9, 130.0, 128.3, 127.9, 118.4, 116.4, 16.3.

HRMS: *m*/*z* calcd for $C_{15}H_{13}N_2O$: 237.1022 $[M + H]^+$; found: 237.1023.

4-Methyl-3,5,6-triphenylpyridin-2(1*H*)-one (2g)[8b]
White solid; mp 316–318 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.79 (br s, 1 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.29–7.34 (m, 3 H), 7.19–7.24 (m, 8 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 1.71 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.0, 146.2, 137.2, 136.7, 131.2, 130.2, 129.5, 128.2, 128.0, 127.9, 127.6, 126.8, 126.7, 19.7.

ESI-MS: *m*/*z* = 338 (M + 1).

3,5,6-Triphenylpyridin-2(1*H*)-one (2h)
Yellow solid; mp 251–253 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.48 (br s, 1 H), 7.73–7.75 (m, 3 H), 7.29–7.41 (m, 8 H), 7.22–7.25 (m, 3 H), 7.13–7.15 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.5, 142.8, 142.3, 137.9, 135.9, 133.6, 129.6, 129.5, 129.5, 129.2, 128.5, 128.4, 128.4, 128.1, 127.7, 126.9, 119.5.

HRMS: *m*/*z* calcd for $C_{23}H_{18}NO$: 324.1383 $[M + H^+]$; found: 324.1383.

3-Phenylquinolin-2(1*H*)-one (2i)[6a,b]
Light yellow solid; mp 232–234 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.72 (br s, 1 H), 7.92 (s, 1 H), 7.81–7.83 (m, 2 H), 7.61 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.47–7.51 (m, 3 H), 7.40–7.44 (m, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.20–7.24 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.0, 138.4, 138.0, 136.2, 132.5, 130.3, 128.9, 128.3, 128.2, 127.8, 122.7, 120.4, 115.5.

ESI-MS: *m*/*z* = 222 (M + 1).

3-Phenyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (2j)
Yellow solid; mp 238–239 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.11 (br s, 1 H), 7.96 (s, 1 H), 7.90 (s, 1 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 7.44–7.53 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5, 139.9, 137.9, 135.4, 133.9, 128.9, 128.7, 128.4, 126.6, 126.6, 125.3, 125.3, 125.2, 125.1, 124.9, 122.9, 119.7, 116.3.

HRMS: *m*/*z* calcd for $C_{16}H_{11}F_3NO$: 290.0787 $[M + H]^+$; found: 290.0789.

6-Chloro-3-phenylquinolin-2(1*H*)-one (2k)[8c]
Yellow solid; mp 209–210 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.70 (br s, 1 H), 7.83 (s, 1 H), 7.77–7.79 (m, 2 H), 7.59 (d, *J* = 2.0 Hz, 1 H), 7.47–7.51 (m, 2 H), 7.42–7.45 (m, 2 H), 7.29 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7, 137.2, 136.3, 135.6, 133.7, 130.5, 128.9, 128.5, 128.4, 127.9, 126.9, 121.3, 116.9.

ESI-MS: *m*/*z* = 256 (M + 1).

7-Methyl-3-phenylquinolin-2(1*H*)-one (2l)
Yellow solid; mp 233–234 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.03 (br s, 1 H), 7.87 (s, 1 H), 7.79–7.81 (m, 2 H), 7.45–7.50 (m, 3 H), 7.37–7.41 (m, 1 H), 7.12 (s, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.9, 141.1, 138.3, 138.0, 136.3, 131.3, 128.8, 128.2, 128.0, 127.7, 124.3, 118.2, 115.2, 21.8.

ESI-MS: *m*/*z* = 236 (M + 1).

6-Methoxy-3-phenylquinolin-2(1*H*)-one (2m)[6a]
Yellow solid; mp 248–249 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.37 (br s, 1 H), 7.86 (s, 1 H), 7.81 (d, *J* = 8.0 Hz, 2 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 7.28 (s, 1 H), 7.14 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.04 (d, *J* = 2.8 Hz, 1 H), 3.87 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0, 155.2, 137.9, 136.2, 133.0, 132.4, 128.9, 128.3, 128.2, 120.9, 119.8, 116.4, 109.1, 55.7.

ESI-MS: *m*/*z* = 252 (M + 1).

6-Phenylfuro[3,2-*b*]pyridin-5(4*H*)-one (2n)
Yellow solid; mp 139–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.28 (br s, 1 H), 7.84 (s, 1 H), 7.76 (d, *J* = 7.6 Hz, 2 H), 7.60 (d, *J* = 1.6 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.37 (t, *J* = 7.2 Hz, 1 H), 6.63 (d, *J* = 1.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 147.0, 140.1, 137.1, 132.2, 128.9, 128.2, 127.2, 126.4, 125.5, 102.4.

HRMS: *m*/*z* calcd for $C_{13}H_{10}NO_2$: 212.0706 $[M + H]^+$; found: 212.0709.

6-Phenylthieno[3,2-*b*]pyridin-5(4*H*)-one (2o)
Yellow solid; mp 217–219 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.19 (br s, 1 H), 7.97 (s, 1 H), 7.78 (d, *J* = 7.2 Hz, 2 H), 7.53 (d, *J* = 5.2 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.38 (t, *J* = 7.2 Hz, 1 H), 7.11 (d, *J* = 5.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 142.0, 136.7, 133.4, 130.2, 128.8, 128.3, 128.2, 127.8, 119.2, 117.1.

HRMS: *m*/*z* calcd for $C_{13}H_{10}NOS$: 228.0478 [M + H]$^+$; found: 228.0481.

4-Hydroxy-3-phenylquinolin-2(1*H*)-one (2p)[6a]
White solid; mp 273–275 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.41 (br s, 1H), 10.01 (br s, 1 H), 7.89 (d, *J* = 7.6 Hz, 1 H), 7.45 (t, *J* = 7.2 Hz, 1 H), 7.33–7.35 (m, 4 H), 7.23–7.25 (m, 2 H), 7.13 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.6, 157.3, 138.0, 133.3, 131.1, 130.5, 127.6, 126.8, 123.1, 121.0, 115.4, 114.9, 112.6.

ESI-MS: *m*/*z* = 238 (M + 1).

4-Amino-3-phenylquinolin-2(1*H*)-one (2q)[6a,8d]
Yellow solid; mp 325–326 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.00 (br s, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.42–7.47 (m, 3 H), 7.29–7.33 (m, 3 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 5.85 (br s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.6, 148.4, 138.4, 135.1, 131.0, 130.1, 128.4, 126.6, 123.1, 120.5, 115.1, 113.5, 106.0.

ESI-MS: *m*/*z* = 237 (M + 1).

3-(4-Fluorophenyl)-4-methylquinolin-2(1*H*)-one (3a)[8c]
White solid; mp 291–292 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.09 (br s, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.46–7.50 (m, 1 H), 7.30–7.33 (m, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.17 (t, *J* = 8.8 Hz, 2 H), 2.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 162.7, 161.3, 145.0, 137.3, 132.1, 132.0, 131.7, 131.3, 130.2, 125.0, 122.5, 120.8, 115.9, 115.3, 115.2, 16.9.

ESI-MS: *m*/*z* = 254 (M + 1).

3-(3-Methoxyphenyl)-4-methylquinolin-2(1*H*)-one (3b)
Yellow solid; mp 204–205 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.86 (br s, 1 H), 7.72–7.74 (m, 1 H), 7.38–7.46 (m, 2 H), 7.29 (d, *J* = 7.6 Hz, 1 H), 7.20–7.24 (m, 1 H), 6.90–6.98 (m, 3 H), 3.85 (s, 3 H), 2.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.0, 159.5, 144.8, 137.5, 132.1, 130.1, 129.2, 124.8, 122.7, 122.3, 120.8, 116.3, 115.8, 113.3, 55.2, 16.8.

HRMS: *m*/*z* calcd for $C_{17}H_{16}NO_2$: 266.1176 [M + H]$^+$; found: 266.1178.

4-Methyl-3-(4-nitrophenyl)quinolin-2(1*H*)-one (3c)
Yellow solid; mp 288–289 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.02 (br s, 1 H), 8.35 (d, *J* = 8.4 Hz, 2 H), 7.78 (d, *J* = 8.4 Hz, 1 H), 7.51–7.55 (m, 3 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 2.38 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0, 147.4, 145.6, 143.0, 137.4, 131.6, 130.9, 130.2, 125.2, 123.5, 122.9, 120.5, 116.0, 17.0.

HRMS: *m*/*z* calcd for $C_{16}H_{13}N_2O_3$: 281.0921 [M + H]$^+$; found: 281.0919.

4-Methyl-3-(1-methyl-1*H*-indol-3-yl)quinolin-2(1*H*)-one (3d)
Yellow solid; mp 271–272 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.58 (br s, 1 H), 7.77 (d, *J* = 7.6 Hz, 1 H), 7.36–7.46 (m, 3 H), 7.30 (s, 1 H), 7.21–7.28 (m, 3 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 3.90 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.0, 145.1, 137.0, 136.8, 130.1, 129.6, 128.0, 124.9, 122.3, 121.5, 121.3, 120.5, 119.5, 115.6, 109.5, 108.8, 33.0, 17.6.

HRMS: *m*/*z* calcd for $C_{19}H_{17}N_2O$: 289.1335 [M + H]$^+$; found: 289.1340.

4-Methyl-3-(pyridin-3-yl)quinolin-2(1*H*)-one (3e)
Yellow solid; mp 230–232 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.87 (br s, 1 H), 8.56 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.47 (d, *J* = 1.6 Hz, 1 H), 7.82 (d, *J* = 7.6 Hz, 1 H), 7.70–7.73 (m, 1 H), 7.52–7.56 (m, 1 H), 7.47 (dd, *J* = 7.6, 5.2 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.23–7.26 (m, 1 H), 2.29 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.8, 150.7, 148.2, 144.4, 138.0, 137.9, 132.0, 130.3, 128.6, 125.4, 122.9, 121.9, 119.7, 115.2, 16.6.

HRMS: *m*/*z* calcd for $C_{15}H_{13}N_2O$: 237.1022 [M + H]$^+$; found: 237.1026.

4-Methyl-3-(pyridin-2-yl)quinolin-2(1*H*)-one (3f)
Yellow solid; mp 236–238 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.83 (br s, 1 H), 8.66 (d, *J* = 4.8 Hz, 1 H), 7.85 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.81 (d, *J* = 7.6 Hz, 1 H), 7.52–7.56 (m, 1 H), 7.35–7.41 (m, 3 H), 7.22–7.26 (m, 1 H), 2.22 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.8, 155.3, 148.9, 144.4, 138.0, 135.9, 131.3, 130.3, 125.9, 125.3, 122.3, 121.8, 119.7, 115.2, 16.0.

HRMS: *m*/*z* calcd for $C_{15}H_{13}N_2O$: 237.1022 [M + H]$^+$; found: 237.1024.

1-Cyclopropyl-4-methyl-3-phenylquinolin-2(1*H*)-one (3g)
White solid; mp 159–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.4 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.43–7.47 (m, 2 H), 7.35–7.38 (m, 1 H), 7.29 (d, *J* = 7.6 Hz, 3 H), 3.00 (m, 1 H), 2.33 (s, 3 H), 1.36 (m, 2 H), 0.95 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.9, 142.2, 140.0, 136.4, 132.7, 130.2, 129.4, 128.0, 127.3, 125.3, 121.9, 121.7, 115.4, 26.4, 16.8, 10.5.

HRMS: *m*/*z* calcd for $C_{19}H_{18}NO$: 276.1383 [M + H]$^+$; found: 276.1381.

4-Methyl-1,3-diphenylquinolin-2(1*H*)-one (3h)
Yellow solid; mp 183–184 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 2 H), 7.47–7.51 (m, 1 H), 7.41–7.45 (m, 2 H), 7.31–7.36 (m, 6 H), 7.24–7.28 (m, 1 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 2.44 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6, 143.2, 140.1, 138.1, 136.1, 132.7, 130.4, 129.9, 129.6, 129.0, 128.6, 128.0, 127.4, 125.3, 122.2, 121.3, 116.1, 17.1.

HRMS: *m*/*z* calcd for $C_{22}H_{18}NO$: 312.1383 [M + H]$^+$; found: 312.1383.

4-Methyl-3-phenyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (4a)
White solid; mp 276–277 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.79 (br s, 1 H), 8.00 (s, 1 H), 7.65 (d, *J* = 8.8 Hz, 1 H), 7.49–7.53 (m, 2 H), 7.43–7.46 (m, 1 H), 7.29–7.34 (m, 3 H), 2.39 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 144.6, 139.5, 135.3, 133.6, 130.1, 128.4, 128.0, 126.4, 126.4, 122.6, 120.5, 116.7, 16.9.

HRMS: *m*/*z* calcd for $C_{17}H_{13}F_3NO$: 304.0944 [M + H]$^+$; found: 304.0941.

6-Fluoro-4-methyl-3-phenylquinolin-2(1*H*)-one (4b)
White solid; mp 306–307 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.66 (br s, 1 H), 7.49 (t, *J* = 7.2 Hz, 2 H), 7.38–7.44 (m, 2 H), 7.33 (d, *J* = 7.2 Hz, 2 H), 7.18–7.21 (m, 2 H), 2.31 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7, 159.1, 157.2, 143.9, 135.7, 133.9, 133.3, 130.2, 128.3, 127.7, 121.8, 121.7, 118.2, 118.0, 117.6, 117.6, 110.3, 110.1, 17.0.

HRMS: *m/z* calcd for $C_{16}H_{13}FNO$: 254.0976 $[M + H]^+$; found: 254.0974.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

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(2) (a) Chung, H. S.; Woo, W. S. *J. Nat. Prod.* **2001**, *64*, 1579. (b) Ito, C.; Itoigawa, M.; Furukawa, A.; Hirano, T.; Murata, T.; Kaneda, N.; Hisada, Y.; Okuda, K.; Furukawa, H. *J. Nat. Prod.* **2004**, *67*, 1800. (c) He, J.; Lion, U.; Sattler, I.; Gollmick, F. A.; Grabley, S.; Cai, J.; Meiners, M.; Schünke, H.; Schaumann, K.; Dechert, U.; Krohn, M. *J. Nat. Prod.* **2005**, *68*, 1397.
(3) (a) Oshiro, Y.; Sakurai, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Miwa, T.; Nishi, T. *J. Med. Chem.* **2000**, *43*, 177. (b) Xiao, Z.; Waters, N. C.; Woodard, C. L.; Li, Z.; Li, P.-K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2875. (c) Chilin, A.; Marzano, C.; Guiotto, A.; Baccichetti, F.; Carlassare, F.; Bordin, F. *J. Med. Chem.* **2002**, *45*, 1146. (d) Buchstaller, H.-P.; Siebert, C. D.; Steinmetz, R.; Frank, I.; Berger, M. L.; Gottschlich, R.; Leibrock, J.; Krug, M.; Steinhilber, D.; Noe, C. R. *J. Med. Chem.* **2006**, *49*, 864. (e) Freeman, G. A.; Andrews, C. W.; Hopkins, A. L.; Lowell, G. S.; Schaller, L. T.; Cowan, J. R.; Gonzales, S. S.; Koszalka, G. W.; Hazen, R. J.; Boone, L. R.; Ferris, R. G.; Creech, K. L.; Roberts, G. B.; Short, S. A.; Weaver, K.; Reynolds, D. J.; Milton, J.; Ren, J.; Stuart, D. I.; Stammers, D. K.; Chan, J. H. *J. Med. Chem.* **2004**, *47*, 5923.
(4) (a) Sliskovic, D. R.; Picard, J. A.; Roark, W. H.; Roth, B. D.; Ferguson, E.; Krause, B. R.; Newton, R. S.; Sekerke, C.; Shaw, M. K. *J. Med. Chem.* **1991**, *34*, 367. (b) Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Kitahara, M.; Sakashita, M.; Sakoda, R. *Bioorg. Med. Chem.* **2001**, *9*, 2727. (c) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982. (d) Kumabea, R.; Nishino, H. *Tetrahedron Lett.* **2004**, *45*, 703.
(5) (a) Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281. (b) Jia, C.-S.; Dong, Y.-W.; Tu, S.-W.; Wang, G.-W. *Tetrahedron* **2007**, *63*, 892. (c) Tang, D.-J.; Tang, B.-X.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 6749. (d) Kadnikov, D. V.; Larock, R. C. *J. Organomet. Chem.* **2003**, *687*, 425. (e) Kim, K. H.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1249. (f) Marcaccini, S.; Pepino, R.; Pozo, M. C.; Basurto, S.; Valverde, M. G.; Torroba, T. *Tetrahedron Lett.* **2004**, *45*, 3999. (g) Staskun, B. *J. Org. Chem.* **1964**, *29*, 1153. (h) Marull, M.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 54.
(6) (a) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433. (b) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772. (c) Cortese, N. A.; Ziegler, C. B.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2953.
(7) (a) Wang, D.; Cai, Q.; Ding, K. *Adv. Synth. Catal.* **2009**, *351*, 1722. (b) Cai, Q.; Wei, J.; Fu, L.; Pei, D.; Ding, K. *Org. Lett.* **2010**, *12*, 1500. (c) Chen, H.; Wang, D.; Wang, X.; Huang, W.; Cai, Q.; Ding, K. *Synthesis* **2010**, 1505. (d) Cai, Q.; Li, Z.; Wei, J.; Ha, C.; Pei, D.; Ding, K. *Chem. Commun.* **2009**, 7581. (e) Li, Z.; Fu, L.; Wei, J.; Ha, C.; Pei, D.; Cai, Q.; Ding, K. *Synthesis* **2010**, 3289. (f) Zhou, J.; Fu, L.; Lv, M.; Liu, J.; Pei, D.; Ding, K. *Synthesis* **2008**, 3974.
(8) (a) Wall, M. J.; Player, M. R.; Patch, R. J.; Meegalla, S.; Liu, J.; Illig, C. R.; Cheung, W.; Chen, J.; Asgari, D. PCT Int. Appl. WO 2005009967, **2005**. (b) Wajon, J. F. M.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1957**, *76*, 65. (c) Blackburn, T. P.; Cox, B.; Guildford, A. J.; Le Count, D. J.; Middlemiss, D. N.; Pearce, R. J.; Thornber, C. W. *J. Med. Chem.* **1987**, *30*, 2252. (d) Bergman, J.; Brynolf, A.; Vuorinen, E. *Tetrahedron* **1986**, *42*, 3689.