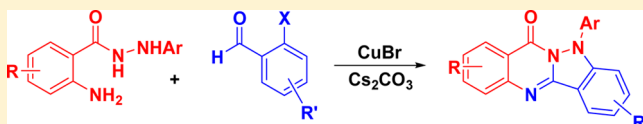


Copper(I)-Catalyzed Synthesis of 5-Arylindazolo[3,2-*b*]quinazolin-7(5*H*)-one via Ullmann-Type ReactionDong-Sheng Chen,[†] Guo-Lan Dou,[‡] Yu-Ling Li,[†] Yun Liu,[†] and Xiang-Shan Wang^{*,†}[†]School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou Jiangsu 221116, PR China[‡]School of Safety Engineering, China University of Mining & Technology, Xuzhou 221116, PR China

S Supporting Information

ABSTRACT: The treatment of 2-amino-*N'*-arylbenzohydrazide and *o*-halogenated benzaldehyde in the presence of CuBr and Cs₂CO₃ gave 5-arylindazolo[3,2-*b*]quinazolin-7(5*H*)-one in high yields. This procedure contains an Ullmann-type reaction and provides an efficient method to construct fused tetracyclic heterocycles.

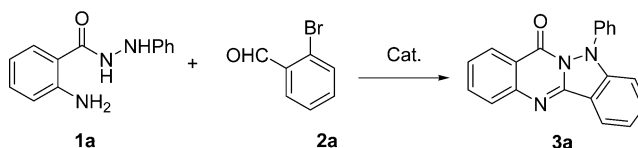


Quinazolinones are important molecules with physiological significance and pharmaceutical utility for their antitumor activity.¹ They are also well-known as the “privileged structures”² for drug design, which are defined as a class of molecules that are capable of binding to multiple receptors with high affinity.³ In addition, indazoles are also good candidates for biological and medicinal purposes, because it is reported that their derivatives are used as glucokinase activators for the treatment of Type 2 diabetes mellitus.⁴ They are also used as mineralocorticoid receptor antagonists,⁵ inhibitors of the PDK1 kinase for treating proliferative disorders⁶ and anticancer agents.⁷ Indazoloquinazoline contains both indazole ring and quinazoline analogue, which may possess novel bioactivity for screening. However, only a few synthetic methods have been reported to synthesize these potentially active fused tetracyclic heterocycles.⁸ Of which, the Pd(PPh₃)₄ mediated reaction of isatoic anhydride, hydrazine, and *o*-iodobenzaldehyde was an efficient procedure to build the indazoloquinazolines.^{8a} In this reported reaction, the scope of the substrate was limited to *o*-iodobenzaldehyde, and expensive metal of Pd was used as catalyst.

It was well-known that Cu(I) was an efficient and inexpensive catalyst for this Ullmann-type reaction.⁹ With this assumption in mind, we tested the two-component reaction of 2-amino-*N'*-arylbenzohydrazide and *o*-halogenated benzaldehyde. It was found that the designed reaction was easy to carry out in the presence of CuBr and Cs₂CO₃ to give 5-arylindazolo[3,2-*b*]quinazolin-7(5*H*)-one derivatives in high yields. Furthermore, the scope of the substrate could be extended from 2-iodobenzaldehyde to various kinds of *o*-bromobenzaldehydes, even to substituted *o*-chlorobenzaldehyde and *o*-fluorobenzaldehyde. Herein, we would like to report the synthesis of 5-arylindazolo[3,2-*b*]quinazolin-7(5*H*)-one via Ullmann-type reaction catalyzed by CuBr.

In our initial study, using the reaction of 2-amino-*N'*-phenylbenzohydrazide **1a** and 2-bromobenzaldehyde **2a** as a model (Scheme 1), several parameters including catalyst, base

Scheme 1. Model Reaction



and solvent were explored as shown in Table 1. No desired product of **3a** was obtained when the reaction was carried out

Table 1. Synthesis of **3a** under Different Reaction Conditions^a

entry	cat (mol %)	solvent	base	yield ^b (%)
1	—	dioxane	Cs ₂ CO ₃	0
2	CuBr (5)	dioxane	—	0
3	CuBr (1)	dioxane	Cs ₂ CO ₃	75
4	CuBr (5)	dioxane	Cs ₂ CO ₃	91
5	CuBr (10)	dioxane	Cs ₂ CO ₃	91
6	CuI (5)	dioxane	Cs ₂ CO ₃	86
7	CuCl (5)	dioxane	Cs ₂ CO ₃	84
8	PdCl ₂ (5)	dioxane	Cs ₂ CO ₃	87
9	Pd(PPh ₃) ₄ (5)	dioxane	Cs ₂ CO ₃	91
10	Pd(OAc) ₂ (5)	dioxane	Cs ₂ CO ₃	85
11	CuBr (5)	dioxane	K ₂ CO ₃	78
12	CuBr (5)	dioxane	NaHCO ₃ ^c	65
13	CuBr (5)	dioxane	Et ₃ N	78
14	CuBr (5)	toluene ^d	Cs ₂ CO ₃	72
15	CuBr (5)	CH ₃ CN	Cs ₂ CO ₃	68
16	CuBr (5)	THF	Cs ₂ CO ₃	65
17	CuBr (5)	DMF ^d	Cs ₂ CO ₃	86

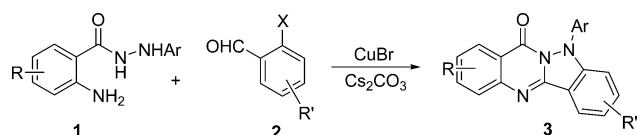
^aReagents and conditions: **1a** (0.227 g, 1.0 mmol), **2a** (0.185 g, 1.0 mmol), solvent (10 mL), base (2.0 mmol), reflux. ^bIsolated yields.

^cNaHCO₃: 4 mmol. ^d100 °C.

Received: February 27, 2013

in the absence of CuBr or base (Table 1, entries 1 and 2), and in the presence of various quantities of CuBr, the yield of product **3a** reached a maximum of 91% with 5 mol % CuBr (Table 1, entries 3–5). Other metal Lewis acids, such as CuI, CuCl, PdCl₂, Pd(PPh₃)₄ and Pd(OAc)₂, were also tested in this reaction (Table 1, entries 6–10); CuBr and Pd(PPh₃)₄ almost gave the same results. Obviously, the catalytic effect of CuBr was better than the rest. Various solvents, such as toluene, CH₃CN, DMF and benzene, and different bases were also tested. Dioxane and Cs₂CO₃ appeared to be the best medium for this transformation (entries 4, 11–17).

Similarly, various kinds of **1** and **2** were tested for this CuBr-catalyzed reaction; they all reacted smoothly to give 5-arylindazolo[3,2-*b*]quinazolin-7(*5H*)-one derivatives in high yields (Scheme 2, Table 2). The results are summarized in

Scheme 2. Reaction of **1** and **2**Table 2. Synthetic Results for the Products **3a**^a

entry	Ar	R	R'	X	products	time (h)	yields ^b (%)
1	Ph	H	H	Br	3a	12	91
2	Ph	H	H	I		11	92
3	Ph	H	5-F	Br	3b	10	86
4	Ph	H	4-F	Br	3c	10	89
5	Ph	H	5-OMe	Br	3d	15	92
6	Ph	H	5-Cl	Br	3e	15	92
7	Ph	H	4,5-(OMe) ₂	Br	3f	16	84
8	Ph	H	4,5-OCH ₂ O	Br	3g	16	90
9	Ph	H	5-NO ₂	Cl	3h	8	84
10	Ph	5-Me	6-Cl	Cl	3i	15	90
11	Ph	5-Me	2-Cl	F		15	85
12	Ph	H	2-Cl	F	3j	10	87
13	Ph	5-Me	H	Br	3k	10	93
14	Ph	5-Me	4-F	Br	3l	12	89
15	Ph	5-Br	H	Br	3m	9	87
16	Ph	4-Cl	H	Br	3n	10	85
17	Ph	5-Cl	H	Br	3o	8	86
18	4-MeC ₆ H ₄	H	4-F	Br	3p	12	88
19	4-MeC ₆ H ₄	H	2-Cl	F	3q	10	91
20	4-ClC ₆ H ₄	H	H	Br	3r	7	90

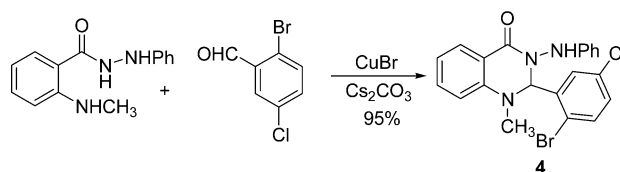
^aReagents and conditions: **1** (1.0 mmol), **2** (1.0 mmol), CuBr (7 mg, 0.05 mmol), Cs₂CO₃ (652 mg, 2 mmol), dioxane (10 mL), reflux.

^bIsolated yields.

Table 2. Of course, 2-iodobenzaldehyde also gave a satisfying result (Table 2, entry 2). Halogen chloride could also act as a leaving group, when 2,6-dichlorobenzaldehyde or 2-chloro-5-nitrobenzaldehyde was used as a reactant (Table 2, entries 9 and 10). Using 2-chloro-6-fluorobenzaldehyde as a starting material, according to our initial assumptions, 4-fluoro-9-methyl-5-phenylindazolo[3,2-*b*]quinazolin-7(*5H*)-one was the product. However, it was found that 4-chloro-9-methyl-5-phenylindazolo[3,2-*b*]quinazolin-7(*5H*)-one was obtained in

86% yields selectively (Table 2, entry 11) with halogen fluorine as a leaving group unexpectedly, which was the same to that of 2,6-dichlorobenzaldehyde. In order to prove this was not a special example, the different **1** were tested to react with 2-chloro-6-fluorobenzaldehyde, and they all gave the same results (Table 2, entries 12 and 19).

To our surprise, the reaction stayed in the stage of 2-(2-bromo-5-chlorophenyl)-1-methyl-3-(phenylamino)-2,3-dihydroquinazolin-4(*1H*)-one **4** in 95% yield, when 2-(methylamino)-*N'*-phenylbenzohydrazide was used as a reactant to react with 2-bromo-5-chlorobenzaldehyde (Scheme 3) at the

Scheme 3. Reaction Including 2-(Methylamino)-*N'*-phenylbenzohydrazide

same reaction conditions. The subsequent C–N coupling reaction did not occur for the unaromatized 2,3-dihydroquinazolin-4(*1H*)-one. Perhaps, this CuBr/Cs₂CO₃-catalyzed Ullmann-type reaction first occurs by aromatization and then coupling reaction.

According to the structures **3**, **4** and the references,⁹ we think that three major events may be involved, which are the formation of dihydroquinazolinone, oxidation of dihydroquinazolinone to quinazolinone by air, and C–N coupling reaction. The key step is the C–N coupling of hydrazine and halide, which has been well reported by Ullmann,^{9a} Buchwald^{9k} and Ma's groups.^{9c} The possible reaction mechanism is outlined in Scheme 4.

In conclusion, we report a novel and efficient method for the synthesis of 5-arylindazolo[3,2-*b*]quinazolin-7(*5H*)-one derivatives using 5 mol % CuBr as catalyst. The procedure includes the advantages of available reactant, inexpensive catalyst and high yields.

EXPERIMENTAL SECTION

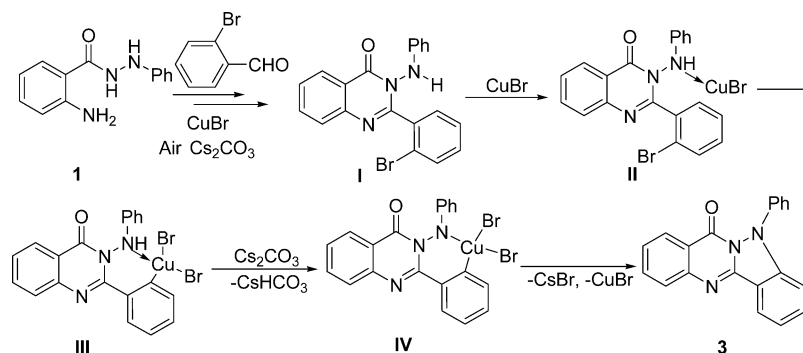
The 2-amino-*N'*-arylbenzohydrazides were prepared according to ref 10.

General Procedure for the Syntheses of 5-Arylindazolo[3,2-*b*]quinazolin-7(*5H*)-one Derivatives **3.** *o*-Halogenated benzaldehyde (1.0 mmol), 2-amino-*N'*-phenylbenzohydrazide (1.0 mmol), CuBr (7 mg, 0.05 mmol), Cs₂CO₃ (652 mg), and dioxane (10 mL) were added into a dry 25 mL flask. The reaction mixture was stirred at reflux for 7–16 h before reaching completion, which was monitored by TLC. The product **3** was purified by column chromatography using ethyl acetate and petroleum ether (1:5) as eluent.

5-Phenylindazolo[3,2-*b*]quinazolin-7(*5H*)-one (3a**).** Yield 91% (284 mg). Pale yellow solid, mp 238–239 °C. ¹H NMR (400 MHz, CDCl₃): δ_H 8.33 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.84–7.80 (m, 1H), 7.64–7.60 (m, 1H), 7.50–7.40 (m, 5H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ_C 156.4, 149.1, 148.6, 148.2, 141.8, 134.0, 133.4, 129.5, 128.6, 127.0, 126.7, 125.4, 124.5, 124.3, 123.2, 119.8, 118.8, 112.4. IR (KBr): ν 3050, 1673, 1626, 1602, 1555, 1486, 1472, 1340, 1302, 1281, 1273, 1242, 1212, 1155, 1111, 1076, 1018, 997, 945, 852, 797, 762, 754, 707, 685 cm⁻¹. HRMS (TOF, ESI, *m/z*): Calcd for C₂₀H₁₄N₃O [M + H]⁺ 312.1137, found 312.1141.

2-Fluoro-5-phenylindazolo[3,2-*b*]quinazolin-7(*5H*)-one (3b**).** Yield 86% (283 mg). Pale yellow solid, mp 267–268 °C. ¹H NMR (400 MHz, CDCl₃): δ_H 8.33 (d, *J* = 8.0 Hz, 1H), 7.94 (dd, *J* = 7.6 Hz,

Scheme 4. Possible Reaction Mechanism



$J' = 2.4$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.85–7.81 (m, 1H), 7.50–7.46 (m, 3H), 7.44–7.40 (m, 1H), 7.38–7.34 (m, 3H), 7.17 (dd, $J = 8.8$ Hz, $J' = 4.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 159.7 (d, $J_{\text{F-C}} = 242.8$ Hz), 156.3, 148.4, 147.6 (d, $J_{\text{F-C}} = 4.4$ Hz), 145.6, 141.8, 134.1, 129.6, 128.8, 127.1, 126.7, 125.7, 124.4, 121.7 (d, $J_{\text{F-C}} = 25.5$ Hz), 119.9 (d, $J_{\text{F-C}} = 10.1$ Hz), 119.8, 114.0 (d, $J_{\text{F-C}} = 8.5$ Hz), 108.8 (d, $J_{\text{F-C}} = 25.1$ Hz). ^{19}F NMR (400 MHz, CDCl_3): δ_{F} -117.7. IR (KBr): ν 3055, 2920, 1678, 1634, 1603, 1556, 1487, 1474, 1344, 1286, 1262, 1245, 1226, 1150, 1131, 1101, 1073, 1008, 962, 890, 862, 818, 807, 768, 754, 704, 688 cm^{-1} . HRMS (TOF, ESI, m/z): Calcd for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{OF}$ $[\text{M} + \text{H}]^+$ 330.1043, found 330.1047.

3-Fluoro-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3c). Yield 89% (293 mg). Pale yellow solid, mp 211–212 °C. ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.32 (d, $J = 8.0$ Hz, 1H), 8.26 (dd, $J = 8.4$ Hz, $J' = 5.2$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.84–7.80 (m, 1H), 7.52–7.42 (m, 4H), 7.36 (d, $J = 7.6$ Hz, 2H), 7.16–7.12 (m, 1H), 6.87 (d, $J = 8.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 166.2 (d, $J_{\text{F-C}} = 251.9$ Hz), 156.2, 150.2 (d, $J_{\text{F-C}} = 12.8$ Hz), 148.6, 147.3, 141.2, 134.1, 129.7, 128.9, 126.9, 126.7, 125.5, 125.2 (d, $J_{\text{F-C}} = 10.9$ Hz), 124.5, 119.5, 114.9 (d, $J_{\text{F-C}} = 1.6$ Hz), 113.1 (d, $J_{\text{F-C}} = 24.6$ Hz), 99.5 (d, $J_{\text{F-C}} = 27.6$ Hz). ^{19}F NMR (400 MHz, CDCl_3): δ_{F} -103.2. IR (KBr): ν 3066, 3012, 1681, 1633, 1604, 1493, 1467, 1442, 1343, 1284, 1265, 1242, 1218, 1180, 1162, 1140, 1096, 1032, 1005, 976, 833, 782, 771, 744, 703, 688 cm^{-1} . HRMS (TOF, ESI, m/z): Calcd for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{OF}$ $[\text{M} + \text{H}]^+$ 330.1043, found 330.1044.

2-Methoxy-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3d). Yield 92% (314 mg). Pale yellow solid, mp 235–236 °C. ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.33 (d, $J = 8.0$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.82 (t, $J = 7.6$ Hz, 1H), 7.66 (d, $J = 2.4$ Hz, 1H), 7.48–7.44 (m, 3H), 7.41–7.37 (m, 1H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.25–7.22 (m, 1H), 7.13 (d, $J = 9.2$ Hz, 1H), 3.94 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 152.0, 151.2, 143.3, 143.2, 138.9, 137.0, 128.8, 124.3, 123.2, 121.6, 121.5, 120.1, 118.9, 118.7, 114.4, 114.1, 108.6, 98.1, 50.8. IR (KBr): ν 3022, 2959, 2935, 1686, 1633, 1602, 1556, 1495, 1417, 1357, 1291, 1275, 1248, 1198, 1189, 1172, 1154, 1101, 1031, 1009, 956, 888, 847, 833, 805, 767, 748, 712, 688 cm^{-1} . HRMS (TOF, ESI, m/z): Calcd for $\text{C}_{21}\text{H}_{16}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 342.1243, found 342.1246.

2-Chloro-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3e). Yield 92% (318 mg). Pale yellow solid, mp 272–273 °C. ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.32 (d, $J = 8.0$ Hz, 1H), 8.23 (s, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.85–7.81 (m, 1H), 7.56 (d, $J = 8.8$ Hz, 1H), 7.50–7.47 (m, 3H), 7.45–7.41 (m, 1H), 7.35 (d, $J = 7.6$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 156.2, 148.4, 147.4, 147.0, 141.4, 134.2, 133.7, 130.1, 129.7, 128.9, 127.1, 126.7, 125.8, 124.5, 122.8, 120.1, 119.8, 113.6. IR (KBr): ν 3047, 3008, 1680, 1628, 1601, 1556, 1490, 1467, 1338, 1317, 1285, 1254, 1232, 1189, 1154, 1144, 1124, 1064, 1009, 953, 872, 817, 797, 767, 753, 729, 700, 689 cm^{-1} . HRMS (TOF, ESI, m/z): Calcd for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{OCl}$ $[\text{M} + \text{H}]^+$ 346.0747, found 346.0741.

2,3-Dimethoxy-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3f). Yield 84% (312 mg). Pale yellow solid, mp 234–235 °C. ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.30 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 7.81–7.77 (m, 1H), 7.61 (s, 1H), 7.51–7.47 (m, 2H), 7.44–

7.40 (m, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 6.57 (s, 1H), 4.03 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 156.4, 155.1, 148.9, 148.6, 147.9, 145.1, 142.1, 133.9, 129.6, 128.6, 126.7, 126.5, 124.8, 124.6, 119.1, 110.1, 102.7, 94.6, 56.6, 56.4. IR (KBr): ν 3008, 2986, 1674, 1633, 1602, 1592, 1555, 1506, 1493, 1464, 1386, 1331, 1272, 1246, 1218, 1191, 1157, 1123, 1105, 1039, 1016, 980, 894, 860, 815, 771, 738, 706 cm^{-1} . HRMS (TOF, ESI, m/z): Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ 372.1348, found 372.1345.

5-Phenyl-[1,3]dioxolo[4',5':5,6]indazolo[3,2-*b*]quinazolin-7(5H)-one (3g). Yield 90% (319 mg). Pale yellow solid, mp >300 °C. ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.29 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 1H), 7.80–7.63 (m, 1H), 7.56 (s, 1H), 7.49–7.45 (m, 2H), 7.43–7.39 (m, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 6.60 (s, 1H), 6.09 (s, 2H, CH_2). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 156.4, 153.5, 148.9, 148.3, 146.5, 146.2, 141.9, 134.0, 129.6, 128.7, 126.7, 126.6, 124.8, 124.5, 119.0, 116.0, 102.5, 100.7, 93.4. IR (KBr): ν 3101, 3053, 2920, 2866, 1674, 1615, 1598, 1556, 1490, 1472, 1413, 1392, 1348, 1325, 1260, 1215, 1151, 1113, 1032, 1005, 979, 924, 889, 837, 784, 768, 704 cm^{-1} . HRMS (TOF, ESI, m/z): Calcd for $\text{C}_{21}\text{H}_{14}\text{N}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ 356.1035, found 356.1040.

2-Nitro-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3h). Yield 84% (299 mg). Pale yellow solid, mp 295–296 °C. ^1H NMR (400 MHz, CDCl_3): δ_{H} 9.21 (d, $J = 1.6$ Hz, 1H), 8.48 (dd, $J = 8.8$ Hz, $J' = 2.0$ Hz, 1H), 8.32 (d, $J = 8.0$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.89–7.85 (m, 1H), 7.57–7.51 (m, 4H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.25 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 156.0, 155.6, 148.2, 146.2, 144.3, 139.7, 134.5, 129.9, 129.6, 128.5, 127.4, 126.7, 126.3, 125.2, 120.1, 120.0, 118.8, 112.0. IR (KBr): ν 3064, 1686, 1631, 1600, 1524, 1489, 1471, 1461, 1341, 1294, 1255, 1232, 1128, 1070, 1008, 959, 797, 767, 738 cm^{-1} . HRMS (TOF, ESI, m/z): Calcd for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ 357.0988, found 357.0969.

1-Chloro-9-methyl-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3i). Yield 90% (324 mg). Pale yellow solid, mp 232–233 °C. ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.09 (s, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.50–7.46 (m, 3H), 7.44–7.40 (m, 1H), 7.36–7.34 (m, 3H), 7.08 (d, $J = 8.4$ Hz, 1H), 2.50 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 156.1, 150.3, 146.6, 146.0, 141.7, 136.1, 135.6, 133.2, 130.8, 129.6, 128.7, 127.7, 125.7, 125.3, 124.6, 119.4, 116.2, 110.6, 21.4. IR (KBr): ν 3481, 3415, 3014, 2914, 1681, 1626, 1602, 1486, 1427, 1332, 1297, 1235, 1152, 1136, 1123, 1063, 1028, 965, 825, 794, 779, 747, 726, 696 cm^{-1} . HRMS (TOF, ESI, m/z): Calcd for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{OCl}$ $[\text{M} + \text{H}]^+$ 360.0904, found 360.0904.

1-Chloro-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3j). Yield 87% (301 mg). Pale yellow solid, mp 263–264 °C. ^1H NMR (400 MHz, CDCl_3): δ_{H} 8.31 (d, $J = 8.4$ Hz, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 7.84–7.81 (m, 1H), 7.51–7.47 (m, 4H), 7.44–7.41 (m, 1H), 7.36 (d, $J = 8.0$ Hz, 3H), 7.07 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 156.2, 150.3, 148.5, 146.6, 141.5, 133.9, 133.4, 131.0, 129.6, 128.9, 127.9, 126.4, 125.9, 125.4, 124.8, 119.6, 116.0, 110.6. IR (KBr): ν 3046, 1691, 1599, 1554, 1468, 1425, 1335, 1293, 1252, 1236, 1154, 1105, 1002, 964, 789, 763, 723 cm^{-1} . HRMS (TOF, ESI, m/z): Calcd for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{OCl}$ $[\text{M} + \text{H}]^+$ 346.0747, found 346.0727.

9-Methyl-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3k). Yield 93% (302 mg). Pale yellow solid, mp 235–236 °C. ^1H NMR

(400 MHz, CDCl₃): δ_{H} 8.27 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.66–7.59 (m, 2H), 7.49–7.46 (m, 2H), 7.43–7.38 (m, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.4 Hz, 1H), 2.50 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 156.3, 149.0, 147.6, 146.6, 141.9, 135.7, 135.6, 133.2, 129.5, 128.4, 126.8, 126.0, 124.3, 123.1, 119.6, 118.9, 112.4, 21.4. IR (KBr): ν 3050, 3015, 1671, 1630, 1606, 1488, 1465, 1344, 1301, 1273, 1237, 1213, 1152, 1107, 1077, 1036, 1002, 957, 883, 822, 777, 769, 752, 708, 696 cm⁻¹. HRMS (TOF, ESI, m/z): Calcd for C₂₁H₁₆N₃O [M + H]⁺ 326.1293, found 326.1293.

3-Fluoro-9-methyl-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3l). Yield 89% (306 mg). Pale yellow solid, mp 220–221 °C. ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.25–8.22 (m, 1H), 8.10 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.51–7.48 (m, 2H), 7.45–7.41 (m, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.14–7.10 (m, 1H), 6.87 (d, J = 8.8 Hz, 1H), 2.50 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 166.1 (d, $J_{\text{F-C}}$ = 251.4 Hz), 156.2, 150.2 (d, $J_{\text{F-C}}$ = 12.8 Hz), 146.8, 146.6, 141.4, 135.8, 135.7, 129.7, 128.8, 126.7, 126.0, 125.1 (d, $J_{\text{F-C}}$ = 10.9 Hz), 124.4, 119.3, 115.1 (d, $J_{\text{F-C}}$ = 1.6 Hz), 113.1 (d, $J_{\text{F-C}}$ = 24.5 Hz), 99.5 (d, $J_{\text{F-C}}$ = 27.7 Hz), 21.4. ¹⁹F NMR (400 MHz, CDCl₃): δ_{F} –103.6. IR (KBr): ν 3057, 1683, 1632, 1606, 1491, 1458, 1443, 1379, 1336, 1286, 1224, 1153, 1099, 1076, 1037, 1002, 975, 940, 903, 874, 831, 816, 777, 749, 737, 708 cm⁻¹. HRMS (TOF, ESI, m/z): Calcd for C₂₁H₁₅N₃OF [M + H]⁺ 344.1199, found 344.1197.

9-Bromo-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3m). Yield 87% (339 mg). Pale yellow solid, mp 273–274 °C. ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.44 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.87 (dd, J = 8.8 Hz, J' = 2.0 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.66–7.62 (m, 1H), 7.51–7.47 (m, 2H), 7.44–7.41 (m, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 155.1, 149.0, 148.4, 147.4, 141.4, 137.1, 133.7, 129.6, 129.1, 128.8, 128.7, 124.52, 124.49, 123.2, 121.0, 118.6, 118.5, 112.3. IR (KBr): ν 3054, 1672, 1623, 1593, 1543, 1494, 1469, 1342, 1300, 1263, 1208, 1153, 1126, 1076, 1026, 950, 892, 826, 806, 749 cm⁻¹. HRMS (TOF, ESI, m/z): Calcd for C₂₀H₁₃N₃OBr [M + H]⁺ 390.0242, found 390.0228.

10-Chloro-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3n). Yield 85% (294 mg). Pale yellow solid, mp 208–209 °C. ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.27 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.90 (s, 1H), 7.66–7.63 (m, 1H), 7.51–7.47 (m, 2H), 7.45–7.39 (m, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 155.8, 149.6, 149.1, 149.0, 141.4, 140.2, 133.8, 129.6, 128.7, 128.1, 126.4, 126.0, 124.6, 124.5, 123.4, 118.4, 118.1, 112.3. IR (KBr): ν 3050, 1675, 1626, 1594, 1543, 1485, 1467, 1456, 1329, 1279, 1265, 1121, 1074, 1024, 946, 874, 762, 753 cm⁻¹. HRMS (TOF, ESI, m/z): Calcd for C₂₀H₁₃N₃OCl [M + H]⁺ 346.0747, found 346.0736.

9-Chloro-5-phenylindazolo[3,2-*b*]quinazolin-7(5H)-one (3o). Yield 86% (297 mg). Pale yellow solid, mp 266–267 °C. ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.29 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.45 (dd, J = 8.8 Hz, J' = 2.0 Hz, 1H), 7.68–7.64 (m, 1H), 7.53–7.49 (m, 2H), 7.47–7.43 (m, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 155.3, 149.0, 148.3, 147.1, 141.4, 134.4, 133.6, 131.0, 129.6, 128.7, 128.6, 125.9, 124.54, 124.46, 123.2, 120.6, 118.5, 112.3. IR (KBr): ν 3058, 1673, 1624, 1597, 1545, 1494, 1483, 1471, 1342, 1299, 1265, 1153, 1127, 1074, 829, 806, 759, 751, 701 cm⁻¹. HRMS (TOF, ESI, m/z): Calcd for C₂₀H₁₃N₃OCl [M + H]⁺ 346.0747, found 346.0734.

3-Fluoro-5-(*p*-tolyl)indazolo[3,2-*b*]quinazolin-7(5H)-one (3p). Yield 88% (302 mg). Pale yellow solid, mp 226–227 °C. ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.31 (d, J = 8.4 Hz, 1H), 8.27–8.23 (m, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.83–7.79 (m, 1H), 7.47–7.44 (m, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.12 (t, J = 8.8 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 2.41 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 166.2 (d, $J_{\text{F-C}}$ = 251.7 Hz), 156.3, 150.4 (d, $J_{\text{F-C}}$ = 12.8 Hz), 146.8, 147.3, 139.1, 138.6, 134.1, 130.3, 126.9, 126.7, 125.4, 125.2 (d, $J_{\text{F-C}}$ = 11 Hz), 124.6, 119.5, 114.8 (d, $J_{\text{F-C}}$ = 1.6 Hz), 113.0 (d, $J_{\text{F-C}}$ = 24.5 Hz), 99.4 (d, $J_{\text{F-C}}$ = 27.5 Hz), 21.3. ¹⁹F NMR (400 MHz, CDCl₃): δ_{F} –103.4. IR (KBr): ν 3094, 3064, 1678, 1632, 1603, 1557, 1509, 1492, 1467, 1436, 1344, 1317, 1289, 1266, 1241, 1198, 1163,

1141, 1101, 1005, 974, 951, 839, 818, 762, 707, 685 cm⁻¹. HRMS (TOF, ESI, m/z): Calcd for C₂₁H₁₅N₃OF [M + H]⁺ 344.1199, found 344.1195.

1-Chloro-5-*p*-tolylindazolo[3,2-*b*]quinazolin-7(5H)-one (3q). Yield 91% (327 mg). Pale yellow solid, mp 261–262 °C. ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.31 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.84–7.80 (m, 1H), 7.50–7.46 (m, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.29–7.23 (m, 4H), 7.05 (d, J = 8.4 Hz, 1H), 2.40 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 156.2, 150.5, 148.5, 146.5, 139.0, 138.9, 133.9, 133.3, 130.9, 130.2, 127.9, 126.4, 125.8, 125.2, 124.8, 119.7, 115.9, 110.6, 21.2. IR (KBr): ν 3051, 2920, 1682, 1618, 1599, 1510, 1484, 1466, 1432, 1334, 1301, 1251, 1158, 1136, 1001, 964, 773, 750 cm⁻¹. HRMS (TOF, ESI, m/z): Calcd for C₂₁H₁₅N₃OCl [M + H]⁺ 360.0904, found 360.0896.

5-(4-Chlorophenyl)indazolo[3,2-*b*]quinazolin-7(5H)-one (3r). Yield 90% (311 mg). Pale yellow solid, mp 236–237 °C. ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.32 (d, J = 8.0 Hz, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.85–7.81 (m, 1H), 7.66–7.62 (m, 1H), 7.50–7.42 (m, 4H), 7.31 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 156.4, 148.8, 148.6, 148.0, 140.4, 134.4, 134.2, 133.5, 129.8, 127.1, 126.6, 126.1, 125.6, 124.6, 123.3, 119.7, 118.9, 112.3. IR (KBr): ν 3055, 1683, 1623, 1602, 1556, 1489, 1483, 1340, 1305, 1273, 1140, 1090, 1016, 946, 933, 835, 765, 751 cm⁻¹. HRMS (TOF, ESI, m/z): Calcd for C₂₀H₁₃N₃OCl [M + H]⁺ 346.0747, found 346.0741.

General Procedure for the Syntheses of the Product 4. 2-Bromo-5-chlorobenzaldehyde (0.219 g, 1.0 mmol), 2-(methylamino)-*N'*-phenyl benzohydrazide (0.241 g, 1.0 mmol), CuBr (7 mg, 0.05 mmol), Cs₂CO₃ (652 mg), and dioxane (10 mL) were added into a dry 25 mL flask. The reaction mixture was stirred at reflux for 3 h before reaching completion, which was monitored by TLC. The hot mixture was treated by immediate filtration to remove the catalyst and base. The filtrate was cooled to room temperature, and the product 4 was obtained by filtration without further purification.

2-(2-Bromo-5-chlorophenyl)-1-methyl-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (4). Yield 95% (420 mg). Pale yellow solid, mp 221–222 °C. ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.01 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.36 (s, 1H), 7.29–7.25 (m, 2H), 7.17 (d, J = 8.0 Hz, 1H), 6.97–6.90 (m, 4H), 6.64 (d, J = 8.4 Hz, 1H), 6.39 (s, 1H), 6.36 (s, 1H), 2.93 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ_{C} 162.5, 146.4, 146.2, 138.9, 134.9, 134.4, 134.3, 130.9, 129.3, 129.0, 127.0, 121.9, 121.3, 118.8, 114.2, 114.1, 112.0, 77.6, 35.5. IR (KBr): ν 3277, 3022, 2920, 1649, 1604, 1494, 1457, 1432, 1377, 1319, 1215, 1173, 1162, 1097, 1026, 1012, 751, 720 cm⁻¹. HRMS (TOF, ESI, m/z): Calcd for C₂₁H₁₇N₃OBrClNa [M + Na]⁺ 464.0141, found 464.0137.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ¹H NMR and ¹³C NMR spectra for compounds 3a–r and 4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xswang1974@yahoo.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science foundation of China (20802061, 21104064), a project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions, Qing Lan Project (10QLD008, GSF2011003) and College Industrialization Project (JHB2012-31) of Jiangsu Province for financial support.

REFERENCES

- (1) (a) Abdel Gawad, N. M.; Georgey, H. H.; Youssef, R. M.; El-Sayed, N. A. *Eur. J. Med. Chem.* **2010**, *45*, 6058–6067. (b) Kamal, A.; Vijaya Bharathi, E.; Janaki Ramaiah, M.; Dastagiri, D.; Surendranadha Reddy, J.; Viswanath, A.; Sultana, F.; Pushpavalli, S. N. C. V. L.; Pal-Bhadra, M.; Srivastava, H. K.; Narahari Sastry, G.; Juvekar, A.; Sen, S.; Zingde, S. *Bioorg. Med. Chem.* **2010**, *18*, 526–542. (c) Evarts, J. B.; Ulrich, R. G. Preparation of atropisomers of 2-purinyl-3-tolyl-quinazolinone derivatives as anti-inflammatory and anticancer agents. PCT Int. Appl. WO 2010111432 A1 30 Sep 2010; *Chem. Abstr.* **2010**, *153*, 456375. (d) Wu, H.; Xie, X.; Liu, G. *J. Comb. Chem.* **2010**, *12*, 346–355. (e) Giri, R. S.; Thaker, H. M.; Giordano, T.; Williams, J.; Rogers, D.; Vasu, K. K.; Sudarsanam, V. *Bioorg. Med. Chem.* **2010**, *18*, 2796–2808. (f) Giri, R. S.; Thaker, H. M.; Giordano, T.; Chen, B.; Nuthalapaty, S.; Vasu, K. K.; Sudarsanam, V. *Eur. J. Med. Chem.* **2010**, *45*, 3558–3563. (g) Liu, J.; Ali, S. M.; Ashwell, M. A.; Ye, P.; Guan, Y.; Ng, S.-C.; Palma, R.; Yohannes, D. Preparation of quinazolinone quinazolinone derivatives useful in treatment of proliferative diseases and cancer. PCT Int. Appl. WO 2009002808 A2 31 Dec 2008; *Chem. Abstr.* **2009**, *150*, 98369.
- (2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
- (3) (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfieldt, J. *J. Med. Chem.* **1988**, *31*, 2235–2246. (b) Duarte, C. D.; Barreiro, E. J.; Fraga, C. A. M. *Mini-Rev. Med. Chem.* **2007**, *7*, 1108–1119.
- (4) Pfefferkorn, J. A.; Tu, M.; Filipski, K. J.; Guzman-Perez, A.; Bian, J.; Aspnes, G. E.; Sammons, M. F.; Song, W.; Li, J.-C.; Jones, C. S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7100–7105.
- (5) Lan, P.; Liu, K.; Ogawa, A.; Shen, H.; Yang, C.; Wang, Y.; Beresis, R.; Qi, C. Preparation of 1H-indazole derivatives as mineralocorticoid receptor antagonists. PCT Int. Appl. 2012, WO 2012139495 A1 20121018.
- (6) Bearss, D. J.; Vankayalapati, H.; Sorna, V.; Warner, S. L.; Sharma, S. Preparation of substituted 3-(1H-benzo[d]imidazol-2-yl)-1H-indazole analogs as inhibitors of the PDK1 kinase for treating proliferative disorders. PCT Int. Appl. 2012, WO 2012135799 A1 20121004.
- (7) Isami, S.; Muramatsu, N.; Tanimura, S. Preparation of salts of indazole derivatives as anticancer agents. PCT Int. Appl. 2011, WO 2011158931 A1 20111222.
- (8) (a) Siva Kumar, K.; Mahesh Kumar, P.; Sreenivasa Rao, V.; Jafar, A. A.; Meda, C. L. T.; Kapavarapu, R.; Parsa, K. V. L.; Pal, M. *Org. Biomol. Chem.* **2012**, *10*, 3098–3103. (b) Bhavani, A. K. D.; Reddy, P. S. N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1992**, *31B*, 736–739. (c) Reddy, V. R. K.; Reddy, P. S. N.; Ratnam, C. V. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1992**, *31B*, 499–502. (d) Reddy, V. R. K.; Reddy, P. S. N.; Ratnam, C. V. *Synth. Commun.* **1991**, *21*, 49–61. (e) Reddy, Y. P.; Reddy, G. S.; Reddy, K. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1979**, *18B*, 125–127. (f) Hill, D. T.; Stanley, K. G.; Libsch, S. S.; Loev, B. J. *Heterocycl. Chem.* **1976**, *13*, 1325–1326. (g) Walser, A.; Zally, W. J.; Fryer, R. I. *J. Heterocycl. Chem.* **1974**, *11*, 863–866.
- (9) (a) Feng, Z.; Chen, F.; Zhang, X. *Org. Lett.* **2012**, *14*, 1938–1941. (b) Jiang, M.; Li, M.; Wang, F.; Zhao, Y.; Zhao, F.; Dong, X.; Zhao, W. *Org. Lett.* **2012**, *14*, 1420–1423. (c) Xiong, X.; Jiang, Y.; Ma, D. *Org. Lett.* **2012**, *14*, 2552–2555. (d) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Org. Lett.* **2012**, *14*, 3894–3897. (e) Kavala, V.; Wang, C. C.; Barange, D. K.; Kuo, C. W.; Lei, P. M.; Yao, C. F. *J. Org. Chem.* **2012**, *77*, 5022–5029. (f) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 1274–1277. (g) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672–674. (h) Wang, C.; Li, S.; Liu, H.; Jiang, Y.; Fu, H. *J. Org. Chem.* **2010**, *75*, 7936–7938. (i) Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, Q. *J. Am. Chem. Soc.* **2012**, *134*, 14326–14329. (j) Chen, Z.; Ye, C.; Gao, L.; Wu, J. *Chem. Commun.* **2011**, *47*, 5623–5625. (k) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803–3805. (l) Tanimori, S.; Kobayashi, Y.; Iesaki, Y.; Ozaki, Y.; Kirihata, M. *Org. Biomol. Chem.* **2012**, *10*, 1381–1387. (m) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971. (n) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384.
- (10) Shemchuk, L. A.; Chernykh, V. P.; Kryskiv, O. S. *Russ. J. Org. Chem.* **2008**, *44*, 1006–1008.