Copper-Catalyzed Sequential N-Arylation and Aerobic Oxidation: Synthesis of Quinazoline Derivatives

Qing Liu,[a] Yufen Zhao,[a] Hua Fu,*[a,b] Changmei Cheng*[a]

[a] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. of China
Fax +86(10)62781695; E-mail: fuhua@mail.tsinghua.edu.cn

[b] Key Laboratory of Chemical Biology (Guangdong Province), Graduate School of Shenzhen, Tsinghua University, Shenzhen 518057, P. R. of China

Received: 15.07.2013; Accepted after revision: 06.08.2013

Abstract: A novel and efficient copper-catalyzed cascade method for the synthesis of quinazoline derivatives has been developed. The protocol uses readily available substituted (2-bromophenyl)methylamines and amidine hydrochlorides as the starting materials, inexpensive CuBr as the catalyst, and economical and environment friendly air as the oxidant, and the corresponding quinazoline derivatives were obtained in moderate to good yields. The procedure underwent sequential intermolecular N-arylation, intramolecular nucleophilic substitution and aerobic oxidation.

Key words: copper, N-arylation, aerobic oxidative, cascade reaction, quinazolines

The quinazoline derivatives have shown various biological and pharmacological activities. For example, they have been used as antitubercular, antiviral, anticancer agents,[1] DNA ligands[2] and potent antibacterial agents.[3] Although many approaches to quinazoline derivatives have been developed, they often suffer from some drawbacks such as necessary activating groups,[4] expensive catalysts,[5] multistep synthesis,[6] and harsh reaction conditions.[7] Therefore, it is highly desirable to developed a novel, efficient and practical method for the synthesis of this kind of compounds. Recently, copper-catalyzed coupling reactions have attracted much attention because of low cost, low toxicity and high efficiency of the copper-catalysts[8] and some N-heterocycles including quinazolines were synthesized via the copper-catalyzed coupling strategy by us[9] and other groups.[10] Herein, we report a novel and useful copper-catalyzed approach to quinazoline derivatives.

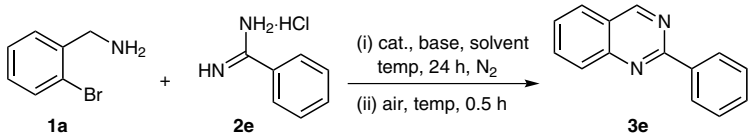
Reaction of (2-bromophenyl)methylamine (**1a**) with benzamidine hydrochloride (**2e**) was chosen as the model reaction to optimize reaction conditions including the catalysts, bases, solvents and temperature. As shown in Table 1, the copper-catalyzed cascade synthesis of 2-phenylquinazoline (**3a**) underwent a sequential two-step procedure: intermolecular N-arylation under N_2 and intramolecular aerobic oxidative dehydrogenation under air. First, four copper catalysts were screened using K_2CO_3 as the base, DMSO as the solvent at 100 °C under N_2 for 24 hours, and then under air for 0.5 hour (entries 1–4), and CuBr exhibited the highest catalytic activity (entry 2). No target product was observed in the absence of copper catalyst (entry 5). Other bases were tested (entries 6–8), and they were inferior to K_2CO_3 (compare entries 2 and 6–8). Affect of solvents was investigated (compare entries 2 and 9–11), and DMSO showed the best result. Different temperature was attempted (entries 12 and 13), and 100 °C was found to be most suitable (compare entries 2, 12 and 13). A lower yield was afforded when the reaction was performed under air for the two steps (N-arylation and oxidation; compare entries 2 and 14). Therefore, the optimum reaction conditions are as follows: CuBr as the catalyst, K_2CO_3 as the base, DMSO as the solvent at 100 °C under N_2 for 24 hours, and then under air for 0.5 hours.

With the optimum reaction conditions in hand, the scope of copper-catalyzed cascade synthesis of quinazoline derivatives was investigated. As shown in Table 2, the tested substrates afforded moderate to good yields. For substituted (2-bromophenyl)methylamines **1**, (2-bromo-4-fluorophenyl)methanamine (**1c**) gave lower yields than (2-bromophenyl)methylamine (**1a**) and (2-bromo-5-methoxyphenyl)methanamine (**1b**). For aromatic amidines, the substrates containing electron-withdrawing groups exhibited lower reactivity than those containing electron-donating groups. Inspiringly, reactions of substituted (2-bromophenyl)methylamines **1** with guanidine hydrochloride (**2j**) also gave better results (entries 10 and 19). The reactions could tolerate some functional groups including C–Cl bond (entries 7 and 17), nitro (entries 8, 9 and 18), ether (entries 11–19), and C–F bond (entries 20–22) in the substrates.

The reaction mechanism for the synthesis of quinazoline derivatives was explored. As shown in Scheme 1, treatment of benzylamine (**4**) with benzamidine hydrochloride (**2e**) was carried out under the standard conditions, and no product **5** was observed. The result showed that the reactions of substituted (2-bromophenyl)methylamines **1** with amidine hydrochlorides **2** did not first start from nucleophilic attack of amino in **1** to carbon in amidine **2** because of weak electrophilic power of amidine group. Therefore,

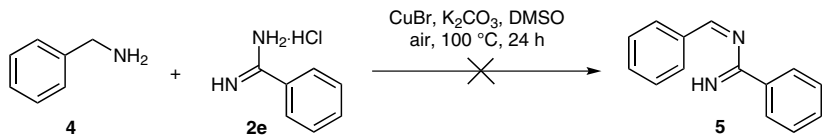
SYNLETT 2013, 24, 2089–2094
Advanced online publication: 27.08.2013
DOI: 10.1055/s-0033-1339800; Art ID: ST-2013-W0652-L

Table 1 Copper-Catalyzed Synthesis of 2-Phenylquinazoline (**3a**) from Reaction of (2-Bromophenyl)methylamine (**1a**) with Benzamidine Hydrochloride (**2e**): Optimization of Conditions[a]

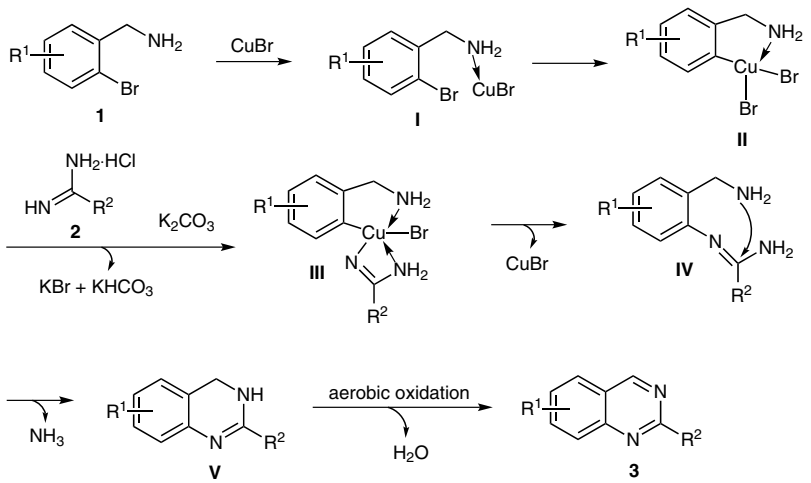


Entry	Catalyst	Base	Solvent	Temp (°C)	Yield (%)[b]
1	CuI	K_2CO_3	DMSO	100	87
2	**CuBr**	**K_2CO_3**	**DMSO**	**100**	**92**
3	$Cu(OAc)_2$	K_2CO_3	DMSO	100	84
4	Cu	K_2CO_3	DMSO	100	88
5	–	K_2CO_3	DMSO	100	trace
6	CuBr	Cs_2CO_3	DMSO	100	32
7	CuBr	Na_2CO_3	DMSO	100	70
8	CuBr	Et_3N	DMSO	100	36
9	CuBr	K_2CO_3	dioxane	100	16
10	CuBr	K_2CO_3	toluene	100	65
11	CuBr	K_2CO_3	DMA	100	83
12	CuBr	K_2CO_3	DMSO	70	79
13	CuBr	K_2CO_3	DMSO	130	59
14	CuBr	K_2CO_3	DMSO	100	64[c]

[a] Reaction conditions: (2-bromophenyl)methylamine (**1a**; 0.5 mmol), benzamidine hydrochloride (**2e**; 1.0 mmol), catalyst (0.1 mmol), base (1.5 mmol), solvent (2 mL), under N_2 for the first step, under air for the second step.
[b] Isolated yield.
[c] The reaction was carried out under air for the two steps.



Scheme 1 Treatment of benzylamine (**4**) with benzamidine hydrochloride (**2e**) under the standard conditions

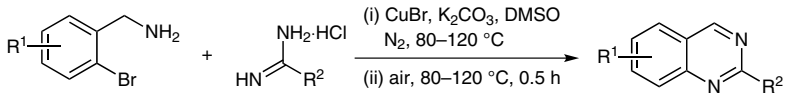


Scheme 2 Possible mechanism for the synthesis of quinazoline derivatives **3**

a possible mechanism for the synthesis of quinazolines is proposed in Scheme 2. Coordination substituted (2-bromophenyl)methylamines **1** with CuBr provides complex **I**, and oxidative addition of **I** leads to **II**. Complexation of **II** with amidine **2** in the presence of base affords **III**, and reductive elimination of **III** gives the N-arylation product **IV** freeing the catalyst (CuBr). Intramolecular nucleophilic attack of amino to carbon of amidine group provides **V** leaving NH_3, and aerobic oxidation of **V** leads to the desired target product **3**.

In summary, we have developed a novel and efficient copper-catalyzed cascade method for the synthesis of quinazoline derivatives.[11] The protocol uses readily available substituted (2-bromophenyl)methylamines and amidine hydrochlorides as the starting materials, inexpensive CuBr as the catalyst, and economical and environment-friendly air as the oxidant, and the corresponding quinazoline derivatives were obtained in moderate to good yields. The procedure underwent sequential intermolecular N-arylation, intramolecular nucleophilic substitution and aerobic oxidation, and the inexpensive, convenient and efficient method for the synthesis of quinazolines will find a wide application in some fields.

Table 2 Copper-Catalyzed Synthesis of Quinazoline Derivatives **3**[a]



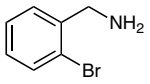
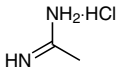
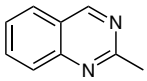
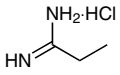
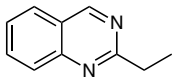
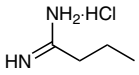
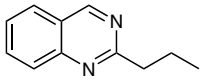
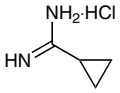
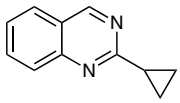
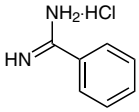
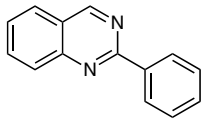
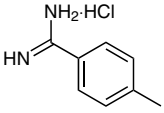
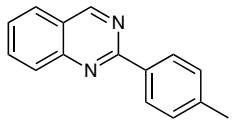
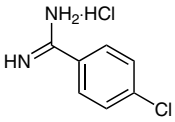
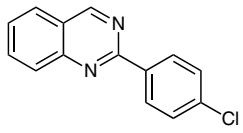
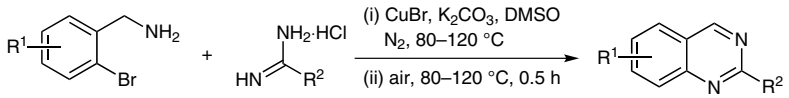
Entry	**1**	**2**	**3** (Temp., Yield[b])
1			
	1a	**2a**	**3a** (100 °C, 73%)
2	**1a**		
		2b	**3b** (100 °C, 62%)
3	**1a**		
		2c	**3c** (100 °C, 60%)
4	**1a**		
		2d	**3d** (100 °C, 94%)
5	**1a**		
		2e	**3e** (100 °C, 92%)
6	**1a**		
		2f	**3f** (100 °C, 99%)
7	**1a**		
		2g	**3g** (100 °C, 73%)

Table 2 Copper-Catalyzed Synthesis of Quinazoline Derivatives **3**[a] (continued)



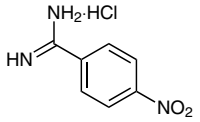
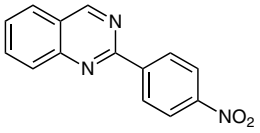
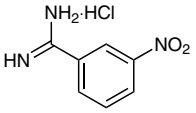
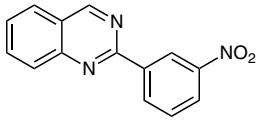
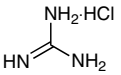
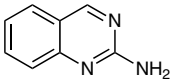
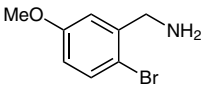
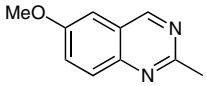
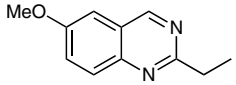
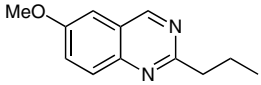
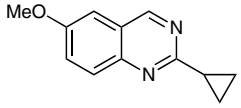
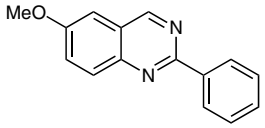
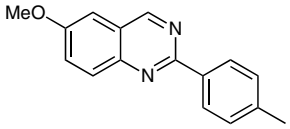
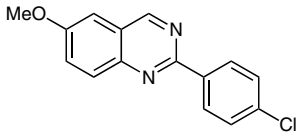
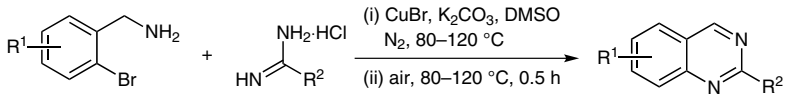
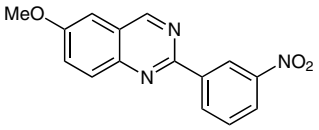
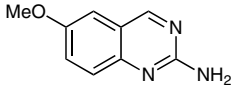
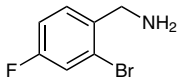
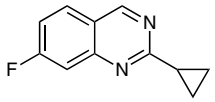
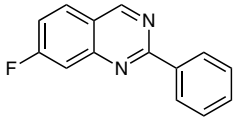
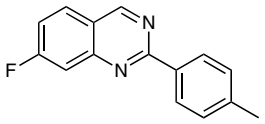
Entry	1	2	3 (Temp., Yield[b])
8	**1a**	 **2h**	 **3h** (100 °C, 40%)
9	**1a**	 **2i**	 **3i** (80 °C, 78%)
10	**1a**	 **2j**	 **3j** (120 °C, 68%)
11	 **1b**	**2a**	 **3k** (100 °C, 60%)
12	**1b**	**2b**	 **3l** (100 °C, 69%)
13	**1b**	**2c**	 **3m** (100 °C, 72%)
14	**1b**	**2d**	 **3n** (100 °C, 85%)
15	**1b**	**2e**	 **3o** (100 °C, 73%)
16	**1b**	**2f**	 **3p** (100 °C, 71%)
17	**1b**	**2g**	 **3q** (100 °C, 67%)

Table 2 Copper-Catalyzed Synthesis of Quinazoline Derivatives **3**[a] (continued)



Entry	1	2	3 (Temp., Yield[b])
18	**1b**	**2i**	 **3r** (80 °C, 65%)
19	**1b**	**2j**	 **3s** (120 °C, 86%)
20	 **1c**	**2d**	 **3t** (100 °C, 55%)
21	**1c**	**2e**	 **3u** (100 °C, 50%)
22	**1c**	**2f**	 **3v** (100 °C, 49%)

[a] Reaction conditions: substituted (2-bromophenyl)methylamine (**1**; 0.5 mmol), amidine hydrochloride (**2**; 1.0 mmol), CuBr (0.1 mmol), K_2CO_3 (1.5 mmol), DMSO (2 mL), reaction temperature (80–120 °C), under N_2 for the first step, under air for the second step.
[b] Isolated yield.

Acknowledgment

The authors wish to thank the National Natural Science Foundation of China (Grant Nos. 21172128 and 21221062), and the Ministry of Science and Technology of China (Grant No. 2012CB722605) for financial support.

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

References and Notes

(1) (a) Foster, A.; Coffrey, H. A.; Morin, M. J.; Rastinejad, F. *Science* **1999**, *286*, 2507. (b) Kunes, J.; Pour, M.; Waisser, K.; Slosarek, M.; Janota, J. *Farmaco* **2000**, *55*, 725. (c) el-Sherbeny, M. A.; Gineinah, M. M.; Nasr, M. N.; el-Shafeith, F. S. *Arzneim.-Forsch.* **2003**, *53*, 206.
(2) Malecki, N.; Caroto, P.; Rigo, B.; Groosens, J. F.; Houssin, R.; Bailly, C.; Henichart, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 641.
(3) Bedi, P. M. S.; Kumar, V.; Mahajan, M. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5211.
(4) Kotsuki, H.; Sakai, H.; Morimoto, H.; Suenaga, H. *Synlett* **1999**, 1993.
(5) (a) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35. (b) Wiedemann, S. H.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2006**, *71*, 1969.
(6) (a) Connolly, D. J.; Cusak, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153. (b) Fekner, T.; Müuller-Bunz, H.; Guiry, P. J. *Org. Lett.* **2006**, *8*, 5109. (c) Coskun, N.; Cetin, M. *Tetrahedron* **2007**, *63*, 2966. (d) Hioki, H.; Matsushita, K.; Nakamura, S.; Horiuchi, H.; Kubo, M.; Harada, K.; Fukuyama, Y. *J. Comb. Chem.* **2008**, *10*, 620.
(7) (a) Ferrini, S.; Ponticelli, F.; Taddei, M. *Org. Lett.* **2007**, *9*, 69. (b) Yoon, D. S.; Han, Y.; Stark, T. M.; Haber, J. C.; Gregg, B. T.; Stankovich, S. B. *Org. Lett.* **2004**, *6*, 4775.
(8) For recent reviews on copper-catalyzed cross-couplings, see: (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13. (b) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954. (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (e) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (f) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (g) Rao, H.; Fu, H. *Synlett* **2011**, 745; and references cited therein.

(9) (a) Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Commun.* **2008**, 6333. (b) Wang, C.; Li, S.; Liu, H.; Jiang, Y.; Fu, H. *J. Org. Chem.* **2010**, *75*, 7936. (c) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 348. (d) Wang, F.; Liu, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2009**, *11*, 2469. (e) Gong, X.; Yang, H.; Liu, H.; Jiang, Y.; Zhao, Y.; Fu, H. *Org. Lett.* **2010**, *12*, 3128. (f) Xu, S.; Lu, J.; Fu, H. *Chem. Commun.* **2011**, *47*, 5596. (g) Liu, T.; Wang, R.; Yang, H.; Fu, H. *Chem. Eur. J.* **2011**, *17*, 6765.

(10) For selected papers on the copper-catalyzed synthesis of N-heterocycles, see: (a) Wu, Z.; Huang, Q.; Zhou, X.; Yu, L.; Li, Z.; Wu, D. *Eur. J. Org. Chem.* **2011**, 5242. (b) Wan, C.; Zhang, J.; Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338. (c) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 2598. (d) Yuan, X.; Xu, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007**, *72*, 1510. (e) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (f) Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079. (g) Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2006**, *8*, 4351. (h) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661. (i) Qu, Y.; Pan, L.; Wu, Z.; Zhou, X. *Tetrahedron* **2013**, *69*, 1717. (j) Liu, T.; Fu, H. *Synthesis* **2012**, *44*, 280; and references cited therein.

(11) **General Procedure for the Synthesis of Compounds 3a–v**: A 25-mL Schlenk tube was charged with a magnetic stirrer and DMSO (2.0 mL). Substituted (2-bromophenyl)methylamine **1** (0.5 mmol), amidine hydrochloride **2** (1.0 mmol), CuBr (0.1 mmol, 14.2 mg), and K_2CO_3 (1.5 mmol, 207 mg) were added to the tube. The mixture was stirred at 80–120 °C under nitrogen atmosphere for 24 h, and then under air for 0.5 h. The resulting mixture was cooled to r.t. and filtered, and the solid was washed with EtOAc three times (3 × 3 mL). The combined filtrate was concentrated by the rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether–EtOAc as eluent to give the desired target product. Three representative examples are shown as follows: **Quinazolin-2-amine (3j)**; (Ref. 12): Eluent: petroleum ether–EtOAc (1:3). Yield: 49.3 mg (68%); yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.10 (s, 1 H), 7.77 (d, J = 8.1 Hz, 1 H), 7.66 (t, J = 7.2 Hz, 1 H), 7.43 (d, J = 8.1 Hz, 1 H), 7.19 (t, J = 7.2 Hz, 1 H), 6.91 (s, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.8, 161.4, 152.3, 134.5, 128.3, 125.0, 122.4, 120.0. ESI–MS: m/z = 146.3 $[M + H]^+$. **2-(4-Chlorophenyl)-6-methoxyquinazoline (3q)**; (Ref. 13): Eluent: petroleum ether–EtOAc (10:1 → 5:1). Yield: 90.5 mg (67%); white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.31 (s, 1 H), 8.50 (d, J = 9.0 Hz, 2 H), 7.95 (d, J = 9.3 Hz, 1 H), 7.54 (dd, J = 9.3, 2.7 Hz, 1 H), 7.47 (d, J = 6.9 Hz, 2 H), 7.11 (d, J = 2.7 Hz, 1 H), 3.95 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 158.5, 147.0, 136.8, 136.4, 130.2, 129.6, 128.9, 127.4, 124.6, 104.0, 55.8. ESI–MS: m/z = 271.2 $[M + H]^+$. **7-Fluoro-2-phenylquinazoline (3u)**; (Ref. 14): Eluent: petroleum ether–EtOAc (10:1). Yield: 56.0 mg (50%); white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 8.59–8.62 (m, 2 H), 7.88–7.91 (m, 1 H), 7.70–7.77 (m, 1 H), 7.51–7.55 (m, 3 H), 7.36–7.40 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0 (J = 255.8 Hz), 161.9, 160.0, 152.5 (d, ^3J = 13.6 Hz), 137.8, 131.1, 129.8 (d, J = 10.8 Hz), 128.8, 121.0, 118.0 (d, J = 25.1 Hz), 112.6 (d, J = 20.8 Hz). ESI–MS: m/z = 225.2 $[M + H]^+$.

(12) Huang, X.; Yang, H.; Fu, H.; Qiao, R.; Zhao, Y. *Synthesis* **2009**, 2679.

(13) Malakar, C. C.; Baskakova, A.; Conrad, J.; Beifuss, U. *Chem. Eur. J.* **2012**, *18*, 8882.

(14) Truong, V. L.; Morrow, M. *Tetrahedron Lett.* **2010**, *51*, 758.

