JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Copper(II)-Catalyzed Hydroxylation of Aryl Halides Using Glycolic acid as a Ligand

Yan Xiao,[†,§] Yongnan Xu,[†] Hwan-Sung Cheon,*[,‡] and Junghyun Chae*[,§]

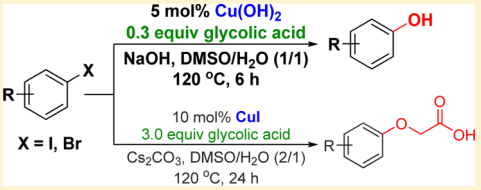
[†]Key Laboratory of Structure-Based Drug Design & Discovery of Ministry of Education, School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang 110016, China

[‡]Central Research Institute, Samsung Cheil Industries Inc., Uiwang-si, Gyeonggi-do 437-711, Korea

[§]Department of Chemistry and Research Institute of Basic Sciences, Sungshin Women's University, Seoul 136-742, Korea

Supporting Information

ABSTRACT: Copper(II)-catalyzed hydroxylation of aryl halides has been developed to afford functionalized phenols. The protocol utilizes the reagent combination of $Cu(OH)_2$, glycolic acid, and NaOH in aqueous DMSO, all of which are cheap, readily available, and easily removable after the reaction. A broad range of aryl iodides and activated aryl bromides were transformed into the corresponding phenols in excellent yields. Moreover, it has been shown that C−O(alkyl)-coupled product, instead of phenol, can be predominantly formed under similar reaction conditions.



Phenols are important structural motifs frequently occurring both in natural products and synthetic chemicals.[1,2] While the oxidative method starting from cumene is the synthetic route currently used for the mass production of phenol,[3,4] several nonoxidative methods are known for the synthesis of functionalized phenols. These conventional methods include nucleophilic aromatic substitution of activated aryl halides,[5] benzyne protocol,[6] and copper-mediated transformation of arene diazonium salts.[7] However, limited availability of starting materials due to the requirement of specific functional groups on the aryl ring and/or harsh reaction conditions considerably hamper their wide use. Alternatively, transition-metal-catalyzed C−O coupling reactions have been sought to synthesize functionalized phenols, but direct hydroxylation of aryl halides has proven to be challenging in contrast to aryl ether synthesis with alkyl alcohols[8,9] and phenols.[10,11]

Recently, several research groups reported palladium-[12−17] and copper-catalyzed[18−24] hydroxylation of aryl halides under relatively mild conditions. In particular, copper catalysts attract more attention as they are cheaper, less toxic, and similarly efficient compared to palladium catalysts. In 2009, it was reported that phenols can be synthesized by direct cross-coupling of hydroxide salts and aryl iodides using CuI and either 1,3-diketone[18] or 1,10-phenanthroline[19] in aqueous DMSO. Subsequently, several other ligands[20−24] such as lithium pipecolinate,[20] 8-hydroxyquinoline-*N*-oxide,[21] and D-glucose[22] were developed, revealing that ligands have great influences on the activity of catalyst systems. Although they provided decent copper-catalyzed protocols for the synthesis of phenols, there is still much room to improve in order to extend its application to wider synthetic fields, especially in industry, where cost- and time-efficiency become more important. For the most reported methods stated above, 10 mol % of CuI is employed along with high loading of expensive ligands except for the one utilizing D-glucose ligand.[22] The choice of bases should not be neglected because bases are often used in excess amounts; some protocols used expensive CsOH as base.[18,21] There was an instance where an extra additive such as quaternary ammonium fluoride was necessary.[20] In another case, the loading of catalyst and ligand should be strictly kept at certain amounts because the reaction yields did not show a linear correlation to the catalyst loadings; higher catalyst loading led to lower yields.[22] In that case, it would be difficult to accelerate the reaction by increasing the catalyst amount. For these reported methods, it was generally found that more than 24 h of reaction time was required for completion. It would be greatly preferred if the same or higher yield could be more reliably obtained by employing less amount of cheaper copper catalysts along with readily available inexpensive ligands and bases. A streamlined synthetic process featuring shorter reaction time, easy workup, and uncomplicated purification of the products would be even more desirable. Herein, we wish to report a fast, scalable, and economical synthesis of functionalized phenols from aryl halides using copper(II) hydroxide as catalyst, glycolic acid as ligand, and NaOH as base in aqueous DMSO. We also demonstrate that a C−O(alkyl) coupling reaction between aryl halides and glycolic acid can be achieved under the slightly modified reaction conditions.

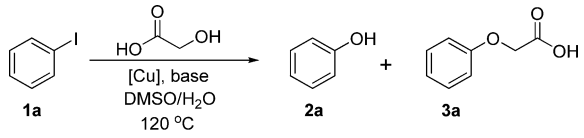
In search for copper-catalyzed reaction conditions for a large-scale synthesis of phenolic intermediates, we realized that copper(II) salts were as effective as copper(I) salts when O,O-donor ligands were used. Among several ligands briefly screened, glycolic acid was identified as a competent ligand. Thus, we set out to investigate copper-catalyzed hydroxylation of aryl halides using glycolic acid by varying copper salts, bases,

Received: April 12, 2013
Published: May 28, 2013

ACS Publications © 2013 American Chemical Society

ligand loadings, reaction time, and temperature (Table 1). When iodobenzene was treated with a variety of copper salts

Table 1. Optimization of Copper-Catalyzed Hydroxylation of Iodobenzene Using Glycolic Acid[a]



1a 2a 3a

entry	G.A. (equiv)	[Cu]	base	time (h)	conv[b] (%)	yield[b] (%) 2a	3a
1	1	CuI	NaOH	20	99	83	16
2	1	CuBr	NaOH	20	100	91	8
3	1	CuCl	NaOH	20	95	74	21
4	1	Cu_2O	NaOH	20	100	95	4
5	1	CuOAc	NaOH	20	96	90	6
6	1	Cu(powder)	NaOH	20	100	99	
7	1	CuO	NaOH	20	100	99	
8	1	$CuCl_2$	NaOH	20	99	98	
9	1	$Cu(OAc)_2$	NaOH	20	94	92	2
10	1	$Cu(OH)_2$	NaOH	20	100	99	
11	1	$CuSO_4$	NaOH	20	99	96	3
12	1	$Cu(OH)_2$	KOH	20	100	99	
13	1	$Cu(OH)_2$	CsOH	20	100	97	
14	0.5	$Cu(OH)_2$	NaOH	6	100	99	
15	0.3	$Cu(OH)_2$	NaOH	6	100	99	
16	0.2	$Cu(OH)_2$	NaOH	6	98	98	
17[c]	0.3	$Cu(OH)_2$	NaOH	12	70	69	
18[d]	0.3	$Cu(OH)_2$	NaOH	6	77	77	
19[e]	3	CuI	Cs_2CO_3	24	95	24	71
20	3	CuI	Cs_2CO_3	24	99	12	87
21	3	CuCl	Cs_2CO_3	24	99	40	58
22	3	Cu_2O	Cs_2CO_3	24	93	35	58
23	3	CuOAc	Cs_2CO_3	24	97	37	60
24	3	$CuCl_2$	Cs_2CO_3	24	87	30	56
25	3	$Cu(OAc)_2$	Cs_2CO_3	24	97	45	52
26	3	$Cu(OH)_2$	Cs_2CO_3	24	94	54	40
27	3	CuI	K_2CO_3	24	65	7	58
28	3	CuI	K_3PO_4	24	60	8	52

[a]Reaction conditions for entries 1−18: 1.0 mmol of PhI, 5 mol % of [Cu], glycolic acid (G.A.), 6.0 equiv of base, DMSO/H_2O (1.5 mL/1.5 mL), 120 °C. Reaction conditions for entries 19−28: 1.0 mmol of PhI, 10 mol % [Cu], glycolic acid, 6.0 equiv base, DMSO/H_2O (2 mL/1 mL), 120 °C. [b]Conversion and yield of **2a** were determined by GC using *n*-dodecane as an internal standard and yield of **3a** was determined by NMR in comparison with **2a**. [c]4.0 equiv of NaOH. [d]100 °C. [e]DMSO/H_2O (1.5 mL/1.5 mL).

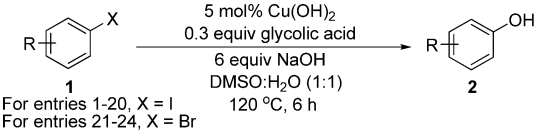
with 1 equiv of glycolic acid in alkaline aqueous DMSO at 120 °C, a considerable amount of phenol was formed regardless of copper sources used (entries 1−11). Interestingly, all of the copper(II) salts and copper powder produced phenol **2a** predominantly without significant formation of byproduct (entries 6−11), whereas most reactions with copper(I) salts produced the coupled product **3a** in as much as 21% yield (entries 1−5). Considering the reactivity observed in the test and many advantages of copper(II) salts over copper(I) salts in terms of cost, air-stability, and water-solubility, we decided to utilize copper(II) salts for the desired conversion. In particular, $Cu(OH)_2$ was chosen for the further optimization as it is one of the least expensive copper(II) salts. Other alkali metal hydroxides such as KOH and CsOH were as effective as NaOH (entries 12 and 13). The concentration of glycolic acid could be reduced down to 30 mol % without loss of the system's reactivity, but further reduction caused incomplete conversion (entries 14−16). Using an excess amount of the base (6 equiv) and an elevated temperature of 120 °C seemed important for the complete conversion (entries 17 and 18). As noticed by other research groups,[18,19,21,22] phenol was best produced in the cosolvent of DMSO and water (1:1). The reactions in the single solvent (DMSO or water) or aqueous solution of other polar aprotic solvents such as DMF, 1,4-dioxane, and NMP were found to be ineffective. Therefore, the optimized conditions for synthesis of phenols are as follows: 5 mol % of $Cu(OH)_2$, 30 mol % of glycolic acid, and 6.0 equiv of NaOH in DMSO−H_2O (1:1) at 120 °C for 6 h.

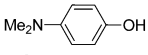
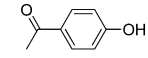
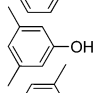
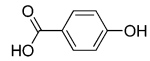
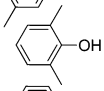
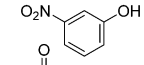
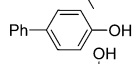
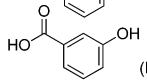
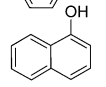
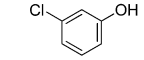
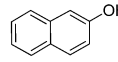
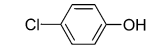
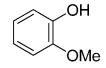
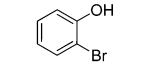
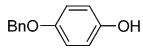
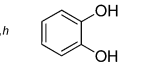
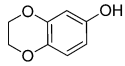
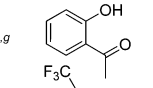
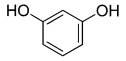
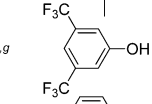
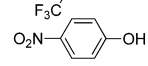
Furthermore, it was revealed that an effective C−O coupling between iodobenzene and glycolic acid occurred affording **3a** when more than 1 equiv of glycolic acid was used with weaker bases (entries 19−28), implying that glycolic acid could play a dual role as both ligand and O-nucleophile. This pathway became more prevailing over phenol generation when solvent contains more DMSO, and we found that **3a** was produced most in 2:1 ratio of DMSO and water (entries 19 and 20). Copper(I) salts are generally more effective than copper(II) salts, and Cs_2CO_3 was found to be the best base probably due to its proper solubility and basicity (entries 20, 27, and 28). Thus, conditions combining CuI with Cs_2CO_3 in DMSO and water (2:1) can be effectively applied for the C−O coupling between aryl iodide and glycolic acid (entry 20).

We then explored the substrate scope of $Cu(OH)_2$/glycolic acid-catalyzed phenol synthesis from aryl halides, and the results are summarized in Table 2. Our catalytic protocol was widely applicable to both electron-rich (entries 2−5, 8−11, 13) and electron-deficient aryl iodides (entries 14−20). Aryl iodides with simple alkyl substituents afforded the corresponding phenols in excellent yields (entries 2−4), and 4-iodobiphenyl and 1- or 2-iodonaphthalene also reacted smoothly (entries 5−7). Remarkably, sterically hindered aryl iodides possessing *ortho*-substituents afforded the hydroxylated products in excellent yields regardless of electronic nature of the substituent (entries 2, 4, 8, and 22). Moreover, our catalytic system showed a great tolerance toward a range of functional groups including hydroxyl, alkoxy, alkylamino,[25] acetyl, carboxylic acid, and nitro (entries 8−11, 13−16). In the case of 3-iodobenzonitrile, the cyano group was fully hydrolyzed to carboxylic acid during the reaction (entry 17). When chloro-substituted aryl iodides were used, hydroxylation took place chemoselectively at the carbon with iodide (entries 18 and 19). Interestingly, 1-bromo-2-iodobenzene was converted largely into 2-bromophenol when 5 mol % of $Cu(OH)_2$ and 6 h of heating was employed (entry 20), but catechol was mainly obtained with 10 mol % of catalyst for a prolonged reaction time (entry 21). Depending on the position of hydroxyl, different results were noticed; *m*-iodophenol was converted into resorcinol in excellent yield, whereas *p*-iodophenol produced the reduction product, phenol (entries 11 and 12). The Taillefer group also reported that *p*- and *o*-iodophenol are not suitable substrates as both are reduced to phenol.[18] Furthermore, we demonstrated that several activated aryl bromides possessing electron-withdrawing groups such as acetyl, trifluoromethyl, and nitro can be applied under the developed conditions, although more catalyst and longer reaction time were needed (entries 22−24).[26] In most high-yielding reactions in Table 2, almost pure products were

dx.doi.org/10.1021/jo400702z | J. Org. Chem. 2013, 78, 5804−5809

Table 2. $Cu(OH)_2$-Catalyzed Synthesis of Phenols[a]



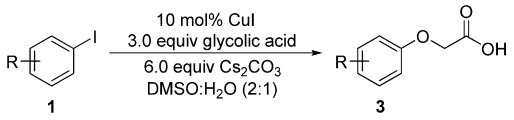
entry	product		yield(%)[b]	entry	product		yield (%)[b]
1		**2a**	99/97[c]	13[f]		**2l**	77
2		**2b**	97	14		**2m**	88
3		**2c**	96	15		**2n**	95
4[d]		**2d**	87	16		**2o**	97
5[e]		**2e**	92	17		**2p** (R=*m*-CN)	99
6		**2f**	90	18		**2q**	98
7		**2g**	94	19		**2r**	99
8[e]		**2h**	95	20		**2s**	92
9		**2i**	94	21[g,h]		**2t** (R=*o*-I)	76
10		**2j**	92	22[e,g]		**2u**	73
11		**2k**	93	23[d,g]		**2v**	85
12		**2a** (R=*p*-OH)	85[i]	24[g]		**2w**	95

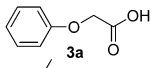
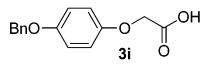
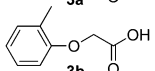
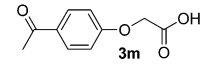
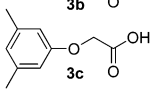
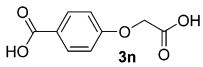
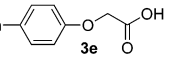
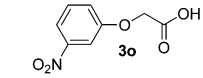
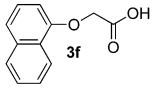
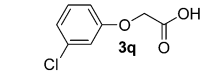
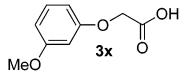
[a]Reaction conditions: 1.0 mmol of aryl iodide, 0.05 equiv of $Cu(OH)_2$, 0.3 equiv of glycolic acid, and 6.0 equiv of NaOH in DMSO/H_2O (1.5 mL/1.5 mL) at 120 °C for 6 h. [b]Isolated yield (average of two runs). [c]20.4 g (100 mmol) scale in 1 M solution. [d]24 h. [e]12 h. [f]8 h. [g]10 mol % of $Cu(OH)_2$. [h]0.5 equiv of glycolic acid for 24 h. [i]Yield refers to the reduction product.

obtained simply by aqueous workup because all the reagents and solvents used in the reaction were water-soluble and easily removed from organic phase. This feature makes the protocol more practical in the large-scale application. In fact, we carried out the synthesis of phenol from iodobenzene in a scale as large as 100 times that of the optimization study to demonstrate the excellent scalability of the developed protocol (entry 1). Iodobenzene (20.4 g, 100 mmol), $Cu(OH)_2$ (0.49 g, 5 mmol), glycolic acid (2.3 g, 30 mmol), and NaOH (24 g, 600 mmol) were stirred in 100 mL of DMSO and H_2O under Ar atmosphere at 120 °C. For this larger scale, the reaction concentration was 1 M, and yet the complete conversion was achieved after 6 h. Concentration of organic layer after acidic aqueous workup afforded 9.2 g of phenol as a pale yellow liquid (97%) whose purity, without further purification, was greater than 98% as determined by ^1H NMR and GC.

As stated previously, we realized that C−O coupling between aryl iodides and glycolic acid can occur under slightly modified conditions. Thus, under the optimized conditions, a variety of aryl iodides were successfully cross-coupled with glycolic acid in good yields regardless of the electronic nature of substituents (Table 3): electron-donating (entries 2−4, 6, 7), electronically neutral (entries 1 and 5), and electron-withdrawing groups

Table 3. CuI-Catalyzed C−O Coupling of Aryl Iodides and Glycolic Acid[a]



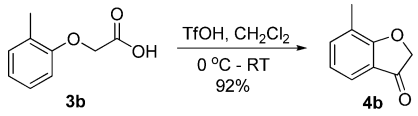
entry	product	yield(%)[b]	entry	product	yield (%)[b]
1	 **3a**	88	7	 **3i**	76
2	 **3b**	82	8[c]	 **3m**	82
3	 **3c**	76	9	 **3n**	84
4	 **3e**	73	10	 **3o**	71
5	 **3f**	70	11	 **3q**	79
6	 **3x**	70			

[a]Reaction conditions: 1.0 mmol of aryl iodide, 0.1 equiv of CuI, 3.0 equiv glycolic acid, and 6.0 equiv Cs_2CO_3 in DMSO/H_2O (2 mL/1 mL) at 120 °C for 24 h. [b]Isolated yield. [c]110 °C for 48 h.

(entries 8−11). Similar to the phenol synthesis, the coupling reaction showed a good tolerance toward various functional groups. Generally, aryl iodides were more than 97% consumed, but 10−25% of phenol was formed in all cases.

Nonetheless, the coupled product **3** can serve as a useful synthetic intermediate because the terminal carboxylic acid can be transformed into other various functional groups. An example is demonstrated in Scheme 1, where one-step

Scheme 1. Synthesis of Benzofuranone 4b from 3b



cyclization of **3b** furnished benzofuranone **4b**.[27] Benzofuranone is a widespread chemical scaffold in natural products, biologically active molecules, and important synthetic intermediates.[28]

In summary, we have developed an efficient, economical, and practical method for the synthesis of functionalized phenols via copper(II)-catalyzed hydroxylation of aryl halides. When compared to previously reported copper-catalyzed hydroxylations, the developed method has the following advantages. (1) Our protocol is very cost-effective. $Cu(OH)_2$, the catalyst of choice, is much cheaper than CuI, and moreover, it is used in lower amounts (5 mol % vs 10 mol %). The protocol avoids any other special ligands or expensive bases by utilizing readily available cheap glycolic acid and NaOH. (2) Nevertheless, the catalytic system is efficient enough so that excellent chemical yields (more than 90% in most cases) were obtained for a broad range of aryl iodides and some activated aryl bromides were also affected under the developed conditions. (3) The protocol is very practical as the reaction time is much shorter (6 h) and product purification is easier. Nearly pure products were

dx.doi.org/10.1021/jo400702z | J. Org. Chem. 2013, 78, 5804−5809

obtained by simple workup because all the reagents are water-soluble and easily removable during aqueous workup. (4) The developed protocol is highly scalable. We successfully carried out a 20 g scale reaction, thereby demonstrating its utility in large-scale preparation. Moreover, we briefly showed that C–O(alkyl) coupling reaction between aryl halides and glycolic acid can be achieved under the slightly modified conditions. Overall, we believe that the developed reaction method should be considered an important advancement in the copper-catalytic preparation of functionalized phenols.

EXPERIMENTAL SECTION

General Considerations. All reagents and solvents were obtained from commercial suppliers and used without purification. The purity of copper catalysts is greater than 97%. Deionized water was used. All manipulations were carried out under Ar. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer (125 MHz for ^{13}C). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quintet), and m (multiplet), and coupling constants (J) are reported in hertz. GC–MS analysis conducted on a GC–MSD system and products described in GC yield were accorded to the authentic samples/*n*-dodecane calibration standard from GC–MSD. Column chromatography was performed on silica gel 60 (230–400 mesh) and TLC was performed on silica gel 60 F_{254} glass plate.

General Procedure for $Cu(OH)_2$-Catalyzed Synthesis of Phenols. A Schlenk tube was charged with aryl halides (**1**) (1.0 mmol), $Cu(OH)_2$ (4.9 mg, 0.05 mmol), glycolic acid (22.8 mg, 0.3 mmol), NaOH (240 mg, 6.0 mmol), and DMSO/H_2O (1.5 mL/1.5 mL). The mixture was stirred at 120 °C for 6 h under Ar. The reaction mixture was allowed to cool to room temperature, poured into 3 mL water, and then acidified to pH = 1 with 2 N HCl. The aqueous phase was extracted twice with EtOAc, and the combined organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. Purification of the crude product by column chromatography (EtOAc/*n*-hexane) afforded the phenols (**2**).

Phenol (**2a**):[18] colorless liquid (93 mg, 99%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.08 (m, 2H), 6.99–6.89 (m, 1H), 6.86–6.78 (m, 2H), 5.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 130.1, 121.3, 115.7.

o-Cresol (**2b**):[21] white solid (105 mg, 97%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14–7.07 (m, 2H), 6.86 (dd, J = 9.5, 5.5 Hz, 1H), 6.78 (dd, J = 8.0, 4.0 Hz, 1H), 4.68 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 131.0, 127.1, 123.7, 120.7, 114.8, 15.7.

3,5-Dimethylphenol (**2c**):[21] pale yellow solid (117 mg, 96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 1H), 6.46 (s, 2H), 4.76 (s, 1H), 2.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 157.6, 94.5, 93.4, 55.6.

2,6-Dimethylphenol (**2d**):[20] white solid (106 mg, 87%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00–6.97 (m, 1H), 6.97–6.95 (m, 1H), 6.75 (t, J = 7.5 Hz, 1H), 4.59 (s, 1H), 2.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 128.8, 123.2, 120.4, 16.1 .

Biphenyl-4-ol (**2e**):[18] white solid (153 mg, 90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.53 (m, 2H), 7.50–7.47 (m, 2H), 7.40 (t, J = 8.0 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 6.92–6.87 (m, 2H), 4.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 140.8, 134.2, 128.7, 128.4, 126.71, 126.70, 115.7.

Naphthalen-1-ol (**2f**):[21] gray solid (130 mg, 90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26–8.11 (m, 1H), 7.80 (dd, J = 5.0, 4.0 Hz, 1H), 7.50–7.38 (m, 3H), 7.27 (dd, J = 8.0, 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 5.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 135.0, 127.9, 126.7, 126.0, 125.5, 124.5, 121.7, 121.0, 108.9.

Naphthalen-2-ol (**2g**):[21] pink solid (135 mg, 94%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (t, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.0 Hz, 1H), 7.33 (t, J = 7.0 Hz, 1H), 7.15 (s, 1H), 7.10 (dd, J = 8.5, 2.5 Hz, 1H), 4.98 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 134.6, 129.8, 128.9, 127.8, 126.5, 126.4, 123.6, 117.7, 109.5.

2-Methoxyphenol (**2h**):[20] yellow solid (118 mg, 95%, 12 h); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (m, 1H), 6.89–6.83 (m, 3H), 5.62 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 145.8, 121.6, 120.3, 114.6, 110.8, 56.0.

4-(Benzyloxy)phenol (**2i**):[29] white solid (188 mg, 94%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.26 (m, 5H), 6.85 (dd, J = 7.5, 5.0 Hz, 2H), 6.74 (dd, J = 8.5, 4.0 Hz, 2H), 5.00 (s, 2H), 4.68 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 149.9, 137.5, 128.8, 128.2, 127.77, 127.76, 116.3, 71.1.

2,3-Dihydrobenzo[b][1,4]dioxin-6-ol (**2j**):[30] colorless liquid (140 mg, 92%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1H), 6.39 (d, J = 3.0 Hz, 1H), 6.33 (dd, J = 8.5, 3.0 Hz, 1H), 4.51 (s, 1H), 4.27–4.17 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 143.9, 136.9, 117.7, 108.4, 104.4, 64.8, 64.3.

Resorcinol (**2k**):[22] white solid (102 mg, 93%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (t, J = 8.0 Hz, 1H), 6.43–6.38 (m, 2H), 6.36 (t, J = 2.5 Hz, 1H), 4.73 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 130.3, 108.1, 103.0.

4-(Dimethylamino)phenol (**2l**):[31] brown solid (105 mg, 77%, 8 h); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (s, 1H), 6.65–6.60 (m, 4H), 2.74 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.6, 144.8, 115.9, 115.3, 42.0.

1-(4-Hydroxyphenyl)ethanone (**2m**):[18] yellow solid (120 mg, 88%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93–7.91 (m, 2H), 7.09–6.75 (m, 2H), 6.45 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 161.0, 131.2, 129.8, 115.5, 26.3.

4-Hydroxybenzoic acid (**2n**):[21] white solid (131 mg, 95%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.42 (s, 1H), 10.21 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.9, 162.2, 132.1, 122.0, 115.8.

3-Nitrophenol (**2o**):[21] yellow solid (135 mg, 97%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.78 (m, 1H), 7.71 (t, J = 2.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.20–7.18 (m, 1H), 5.50 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 149.2, 130.3, 121.9, 115.9, 110.5.

3-Hydroxybenzoic acid (**2p**):[12] white solid (137 mg, 99%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.81 (s, 1H), 9.77 (s, 1H), 7.37–7.27 (m, 3H), 6.99 (d, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.2, 157.3, 131.9, 129.4, 119.8, 119.7, 115.7.

3-Chlorophenol (**2q**):[21] white solid (125 mg, 98%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.86 (s, 1H), 6.76–6.58 (m, 1H), 4.96 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 134.9, 130.5, 121.1, 115.9, 113.7.

4-Chlorophenol (**2r**):[21] colorless liquid (127 mg, 99%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.15 (m, 2H), 6.84–6.69 (m, 2H), 5.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 129.9, 126.1, 117.0.

2-Bromophenol (**2s**):[30] white solid (160 mg, 99%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 10.5, 4.5 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.80 (dd, J = 10.5, 4.5 Hz, 1H), 5.49 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 132.2, 129.3, 122.0, 116.3, 110.4.

Pyrocatechol (**2t**):[22] white solid (84 mg, 76%, 24 h, 10 mol % $Cu(OH)_2$, 0.5 equiv glycolic acid); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, J = 3.5 Hz, 2H), 6.84–6.79 (m, 2H), 5.09 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 121.3, 115.5.

1-(2-Hydroxyphenyl)ethanone (**2u**):[18] yellow solid (100 mg, 73%, 12 h, 10 mol % $Cu(OH)_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.26 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.48 (t, J = 6.5 Hz, 1H), 7.07–6.75 (m, 2H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 162.6, 136.7, 130.9, 120.0, 119.2, 118.7, 26.9.

3,5-Bis(trifluoromethyl)phenol (**2v**):[19] colorless liquid (196 mg, 85%, 24 h, 10 mol % $Cu(OH)_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.28 (s, 2H), 6.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 133.0 (q, J = 33.2 Hz, $-CF_3$), 123.3 (q, J = 271.1 Hz, $-CF_3$), 116.0, 114.3.

4-Nitrophenol (**2w**):[21] yellow solid (132 mg, 95%, 10 mol % $Cu(OH)_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.12 (m, 2H), 7.03–6.87 (m, 2H), 5.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 141.6, 126.3, 115.7.

General Procedure for CuI-Catalyzed C–O Coupling of Aryl Iodides and Glycolic Acid. A Schlenk tube was charged with aryl iodides (**1**) (1.0 mmol), glycolic acid (228 mg, 3.0 mmol), CuI (19.0 mg, 0.1 mmol), Cs_2CO_3 (1.95 g, 6.0 mmol), and DMSO/H_2O (2 mL/

dx.doi.org/10.1021/jo400702z | J. Org. Chem. 2013, 78, 5804–5809

1 mL). The mixture was stirred for 24 h at 120 °C under Ar. The reaction mixture was allowed to cool to room temperature, poured into 5 mL of water, and then acidified to pH = 1 with 2 N HCl solution. The aqueous phase was extracted twice with EtOAc, and the combined organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. Purification of the crude product by column chromatography (dichloromethane/methanol) afforded the desired product (**3**).

*2-Phenoxyacetic acid (**3a**):*[32] white solid (133 mg, 88%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.98 (s, 1H), 7.28 (t, J = 7.0 Hz, 2H), 7.13−6.77 (m, 3H), 4.66 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1, 157.6, 129.3, 120.8, 114.3, 64.2.

*2-(o-Tolyloxy)acetic acid (**3b**):*[33] white solid (125 mg, 82%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.13−7.10 (m, 2H), 6.86−6.78 (m, 2H), 4.67 (s, 2H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 157.4, 132.0, 128.3, 127.3, 122.2, 112.6, 66.1, 17.5.

*2-(3,5-Dimethylphenoxy)acetic acid (**3c**):*[32] white solid (137 mg, 76%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.01 (d, J = 7.5 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 4.34 (s, 2H), 2.21 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 155.9, 131.0, 129.4, 124.7, 69.4, 16.6.

*2-(Biphenyl-4-yloxy)acetic acid (**3e**):*[34] white solid (166 mg, 73%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.60 (t, J = 7.5 Hz, 4H), 7.43 (dd, J = 10.5, 4.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 4.72 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 158.1, 140.4, 133.7, 129.6, 128.4, 127.5, 126.9, 115.6, 65.2.

*2-(Naphthalen-1-yloxy)acetic acid (**3f**):*[32] yellow solid (141 mg, 70%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.13 (s, 1H), 8.26−8.18 (m, 1H), 7.88 (dd, J = 6.5, 2.0 Hz, 1H), 7.58−7.47 (m, 3H), 7.40 (t, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 4.89 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.0, 153.1, 133.9, 127.3, 126.4, 125.9, 125.2, 124.7, 121.5, 120.3, 105.2, 64.8.

*2-(3-Methoxyphenoxy)acetic acid (**3x**):*[35] brown solid (128 mg, 70%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.93 (s, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.67−6.26 (m, 3H), 4.64 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.8, 161.1, 159.6, 130.6, 107.4, 107.2, 101.5, 65.2, 55.8.

*2-(4-(Benzyloxy)phenoxy)acetic acid (**3i**):*[36] gray solid (196 mg, 76%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.93 (s, 1H), 7.45−7.30 (m, 5H), 6.93 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.03 (s, 2H), 4.58 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.1, 153.4, 152.6, 138.0, 129.1, 128.3, 116.3, 116.0, 105.0, 70.3, 65.7.

*2-(4-Acetylphenoxy)acetic acid (**3m**):*[37] yellow solid (160 mg, 82%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 4.78 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 175.0, 166.5, 135.8, 119.3, 104.8, 69.6, 32.1.

*4-(Carboxymethoxy)benzoic acid (**3n**):*[38] white solid (165 mg, 84%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.85 (s, 2H), 7.87 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 4.68 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.7, 166.8, 161.4, 131.1, 123.2, 114.2, 64.8.

*2-(3-Nitrophenoxy)acetic acid (**3o**):*[39] yellow solid (140 mg, 71%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.20 (s, 1H), 7.98−7.77 (m, 1H), 7.70 (s, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.49−7.28 (m, 1H), 4.87 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.6, 158.2, 148.5, 130.6, 121.8, 115.8, 108.8, 64.8.

*2-(3-Chlorophenoxy)acetic acid (**3q**):*[40] white solid (147 mg, 79%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.05 (s, 1H), 7.33−7.29 (m, 7.9 Hz, 1H), 7.15−6.74 (m, 3H), 4.73 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.6, 159.4, 134.3, 131.5, 121.6, 115.3, 114.3, 65.3.

*Synthesis of **2a** in a 100 mmol Scale.* Iodobenzene (20.4 g, 0.1 mol), $Cu(OH)_2$ (0.5 g, 0.005 mol), glycolic acid (2.3 g, 0.03 mol), NaOH (24.0 g, 0.6 mol), DMSO (50 mL), and H_2O (50 mL) were added to a 220 mL round Schlenk flask equipped with a magnetic stirring bar under Ar. The reaction mixture was heated for 6 h at 120 °C. TLC analysis showed the complete conversion of iodobenzene to phenol. The reaction mixture was poured into an ice−water mixture (200 mL), and concentrated HCl (50 mL) was slowly added to bring the pH of the mixture to 1. The aqueous phase was extracted twice with diethyl ether (300 mL), and the combined organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum to afford a pale yellow liquid (9.2 g, 97%).

*Cyclization of **3b**.* Compound **3b** (166 mg, 1.0 mmol) was dissolved in dry CH_2Cl_2 (3 mL), and triflic acid (1.0 mL) was slowly added at 0 °C. Then, the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with ice−water and extracted twice with CH_2Cl_2. The combined organic layer was washed with H_2O and saturated Na_2CO_3 solution, dried over anhydrous $MgSO_4$, and concentrated under vacuum. Purification of the crude product by column chromatography afforded 7-methylbenzofuran-3(2*H*)-one (**4b**) as yellow solid (130 mg, 92%):[41] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.0 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 4.64 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 172.8, 138.2, 123.8, 121.9, 121.3, 120.6, 74.7, 14.2.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: h.s.cheon@samsung.com, jchae@sungshin.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2010-0025089).

■ REFERENCES

(1) Tyman, J. H. P. *Synthetic and Natural Phenols*; Elsevier: New York, 1996.

(2) Rappoport, Z. *The Chemistry of Phenols*; Wiley-VCH: Weinheim, 2003.

(3) Weber, M.; Weber, M.; Kleine-Boymann, M. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag: Weinheim, 2000; pp 503−519.

(4) Hock, H.; Lang, S. *Eur. J. Inorg. Chem.* **1944**, *77*, 257−264.

(5) Zhang, Y. -H.; Yu, J. -Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654−14655.

(6) George, T.; Mabon, R.; Sweeney, G.; Sweeney, J. B.; Tavassoli, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2529−2574.

(7) Cohen, T.; Dietz, A. G.; Miser, J. R. *J. Org. Chem.* **1977**, *42*, 2053−2058.

(8) Das, P.; Sharma, D.; Kumar, M.; Singh, B. *Curr. Org. Chem.* **2010**, *14*, 754−783.

(9) Zhang, H.; Ma, D. W.; Cao, W. G. *Synlett* **2007**, 243−246.

(10) Niu, J.; Zhou, H.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2008**, *73*, 7814−7817.

(11) Alonso, D. A.; Najera, C.; Pastor, I. M.; Yus, M. *Chem.—Eur. J.* **2010**, *16*, 5274−5284.

(12) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694−10695.

(13) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321−4326.

(14) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146−8149.

(15) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718−10719.

(16) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225.

(17) Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 918−921.
(18) Tlili, A.; Xia, N.; Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8725−8728.
(19) Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8729−8732.
(20) Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Zhou, X. *Chem. Commun.* **2010**, *46*, 4767−4769.
(21) Yang, K.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. *Org. Lett.* **2011**, *13*, 4340−4343.
(22) Thakur, K. G.; Sekar, G. *Chem. Commun.* **2011**, *47*, 6692−6694.
(23) Maurer, S.; Liu, W.; Zhang, X.; Jiang, Y.; Ma, D. *Synlett* **2010**, 976−978.
(24) Jia, J.; Jiang, C.; Zhang, X.; Jiang, Y.; Ma, D. *Tetrahedron Lett.* **2011**, *43*, 5593−5595.
(25) For 4-iodo-*N*,*N*-dimethylaniline, the moderate yield was attributed to the formation of water-soluble quaternary ammonium salt and subsequent loss during acidic workup.
(26) It has been reported that such activated aryl bromides poorly react without copper catalyst. See refs 18 and 22.
(27) Prakash, G. K. S.; Yan, P.; Torok, B.; Olah, G. A. *Catal. Lett.* **2003**, *87*, 3−4.
(28) Haudecoeur, R.; Ahmed-Belkacem, A.; Yi, W.; Fortune, A.; Brillet, R.; Belle, C.; Nicolle, E.; Pallier, C.; Pawlotsky, J.-M.; Boumendjel, A. *J. Med. Chem.* **2011**, *54*, 5395−5402.
(29) Ohkubo, M.; Mochizuki, S.; Sano, T.; Kawaguchi, Y.; Okamoto, S. *Org. Lett.* **2007**, *9*, 773−776.
(30) Zhu, C.; Wang, R.; Falck, J. R. *Org. Lett.* **2012**, *14*, 3494−3497.
(31) Stephanopoulos, N.; Carrico, Z. M.; Francis, M. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9498−9502.
(32) Villemin, D.; Hammadi, M. *Synth. Commun.* **1996**, *26*, 4337−4341.
(33) Azzena, U.; Pittalis, M. *Tetrahedron* **2011**, *67*, 3360−3362.
(34) Lee, K.; Goo, J.-I.; Jung, H. Y.; Kim, M.; Boovanahalli, S. K.; Park, H. R.; Kim, M.-O.; Kim, D.-H.; Lee, H. S.; Choi, Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7456−7460.
(35) Carmen Cruz, M. del.; Tamariz, J. *Tetrahedron* **2005**, *61*, 10061−10072.
(36) Spurg, A.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2008**, *73*, 337−342.
(37) Mokale, S. N.; Sanap, P. T.; Shinde, D. B. *Eur. J. Med. Chem.* **2010**, *45*, 3096−3100.
(38) Wang, X.; Li, Z.; Da, Y.; Chen, J.; Wei, T. *Synth. Commun.* **1999**, *29*, 4153−4161.
(39) Hirst, G. C.; Aquino, C.; Birkemo, L.; Croom, D. K.; Dezube, M.; Dougherty, R. W.; Ervin, G. N.; Grizzle, M. K.; Henke, B.; James, M. K.; Johnson, M. F.; Momtahen, T.; Queen, K. L.; Sherrill, R. G.; Szewczyk, J.; Willson, T. M.; Sugg, E. E. *J. Med. Chem.* **1996**, *39*, 5236−5245.
(40) Lin, M.; Zhou, J. M.; Xia, H. P.; Yang, R. F.; Lin, C. *Chem. Res. Chin. U.* **2004**, *20*, 213−215.
(41) Nakano, H.; Saito, N.; Parker, L.; Tada, Y.; Abe, M.; Tsuganezawa, K.; Yokoyama, S.; Tanaka, A.; Kojima, H.; Okabe, T.; Nagano, T. *J. Med. Chem.* **2012**, *55*, 5151−5164.