JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

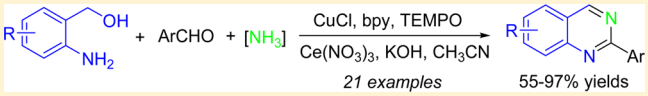
Unexpected Copper-Catalyzed Cascade Synthesis of Quinazoline Derivatives

Zhongyan Chen, Jiuxi Chen,* Miaochang Liu, Jinchang Ding, Wenxia Gao, Xiaobo Huang, and Huayue Wu*

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, China

Supporting Information

ABSTRACT: The first example of a copper-catalyzed cascade reaction of (2-aminophenyl)methanols with aldehydes using the combination of cerium nitrate hexahydrate and ammonium chloride has been developed, leading to a wide range of 2-substituted quinazolines in moderate to excellent yields. The efficiency of this transformation was demonstrated by compatibility with a wide range of functional groups. Thus, the method represents a convenient and practical strategy for synthesis of 2-substituted quinazoline derivatives.



INTRODUCTION

Nitrogen-containing heterocycles are present in a wide variety of bioactive natural products and biological molecules that may be good drug candidates.[1] Specifically, quinazolines and their derivatives represent a medicinally and pharmaceutically important class of heterocyclic motifs that are found as the core structural skeletons in a variety of drug molecules such as prazosin,[2] lapatinib,[3] and icotinib[4] (Figure 1). They possess a wide range of biological and pharmacological activities including anticancer,[5] antiviral,[6] antitubercular,[7] and antimalarial properties.[8] Yang and co-workers[9] recently reported that substituted quinazolines have novel potent and selective FLT3 inhibitory and anti-acute myeloid leukemia (AML) activities. Therefore, the development of different synthetic strategies for the preparation of substituted quinazolines has received much attention. Fu and co-workers[10] reported that copper-catalyzed cascade reactions have provided attractive and valuable routes for the construction of quinazoline derivatives via sequential Ullmann-type coupling and intramolecular cyclization. Walton and co-workers[11] reported microwave-promoted synthesis of quinazolines by the reaction of 2-(aminoaryl)alkanone *O*-phenyl oximes with aldehydes. Tandem reactions of condensation of 2-aminobenzophenones with benzylic amines followed by C−H functionalization have also been reported.[12] In 2012, Zhang et al.[13a] and Saha and co-workers[13b] independently reported direct access to quinazolines from a three-component reaction involving 2-aminobenzophenones, aldehydes, and ammonium acetate. Very recently, Beifuss and co-workers[14] developed a copper-catalyzed synthesis of quinazolines in water, starting from *o*-bromobenzyl bromides and benzamidines. The condensation of 2-(aminomethyl)-benzenamines with aldehydes has been followed by subsequent oxidation in the presence of strong oxidants such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or tetrachloro-1,4-benzoquinone (TCQ),[15a] MnO_2,[15b] and NaClO[15c] (Scheme 1a). However, these methods are hampered by the need to use a stoichiometric amount of a nonrenewable oxidant and the yields have not been satisfactory. To the best of our knowledge, two improved methods have been reported for constructing quinazolines.[16] In 2012, Han et al.[16a] reported the copper-catalyzed aerobic oxidative reaction of 2-(aminomethyl)-benzenamines with aldehydes for the synthesis of quinazolines. In 2013, Zhou and co-workers[16b] reported an iridium-catalyzed hydrogen-transfer reaction of 2-(aminomethyl)benzenamines with aldehydes leading to quinazolines, using styrene as a hydrogen acceptor.

Although the synthesis of 4*H*-benzo[*d*]1,3-oxazines by reaction of (2-aminophenyl)methanols with aldehydes has been investigated extensively in the past (Scheme 1b),[15c,16a,17] this kind of multicomponent reaction still remains a challenging research area. To the best of our knowledge, no reports of copper-catalyzed cascade reaction of (2-aminophenyl)-methanols with aldehydes in the presence of an ammonia source have appeared in the literature. This work forms part of the continuing efforts in our laboratory toward the development of new methods for copper-catalyzed chemistry[18] and the synthesis of quinazolinone derivatives (Scheme 1c).[19] Herein, we report an unexpected copper-catalyzed method for the cascade synthesis of quinazolines by use of readily available (2-aminophenyl)methanols and aldehydes in the presence of an ammonia source (Scheme 1d).

RESULTS AND DISCUSSION

Our preliminary studies focused on the reaction between (2-aminophenyl)methanol (**1a**) and *p*-chlorobenzaldehyde (**2a**) to obtain 2-phenyl-4*H*-benzo[*d*]1,3-oxazine (**4a**) (Scheme 2). Through the screening process, no target product was detected with $Pd(OAc)_2$ as catalyst with a variety of parameters. To our surprise, the trace of unexpected 2-phenylquinazoline (**3a**) was observed by gas chromatography/mass spectrometry (electron ionization) [GC/MS (EI)] analysis during the process of

Received: August 28, 2013
Published: October 17, 2013

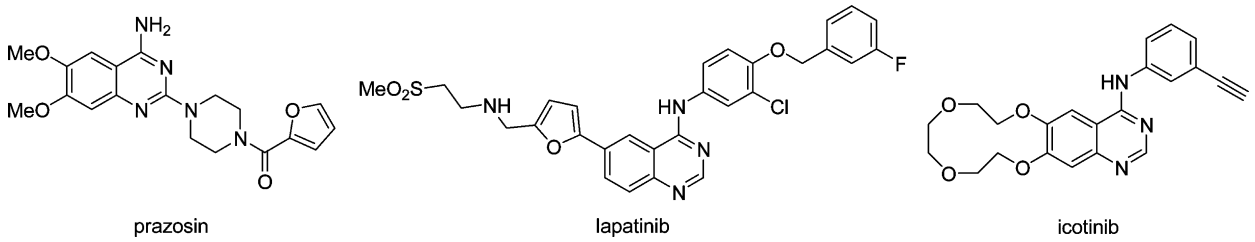
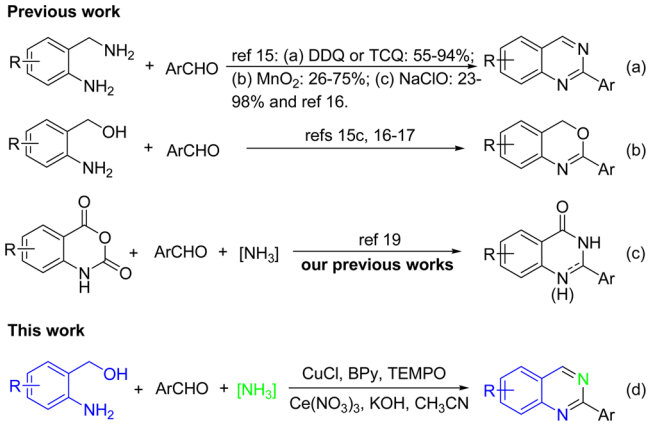
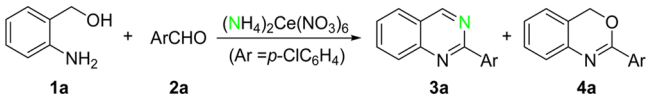


Figure 1. Structures of some biologically active quinazoline cores.

Scheme 1



Scheme 2



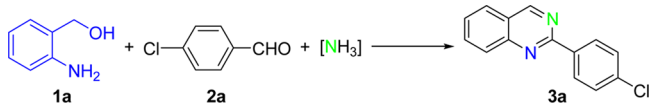
performing the above condensation reaction in the presence of ceric ammonium nitrate (CAN). This finding inspired us to examine optimal reaction conditions for the synthesis of **3a** in order to obtain more satisfactory results. Subsequently, a series of trial experiments was performed in the presence of palladium catalysts by adjusting the reaction parameters. However, little to no product **3a** was detected.

We next investigated the model reaction using copper salts as the catalyst. We were delighted to find that the desired product **3a** was isolated in 32% yield in the presence of CuOTf when the combination of Li_2CO_3 and CAN was employed in CH_3CN (Table 1, entry 1). Encouraged by this promising result, we further adjusted reaction parameters including the copper catalysts, cerium sources, ammonia sources, bases, and solvents. Screening revealed that the use of KOH as base achieved the best result. Other bases, including K_2CO_3, KF, ^{t}BuOK, and K_3PO_4, were less efficient (Table 1, entries 2−6). Among the copper sources used, CuCl exhibited the highest catalytic reactivity with 71% yield (Table 1, entries 6−15). We were pleased to discover that the yield of desired product **3a** could be improved to 90% when the combination of cerium nitrate hexahydrate and ammonium chloride instead of CAN was employed in CH_3CN (Table 1, entry 16). The reaction with combinations of other cerium salts and ammonium chloride as the ammonia source did not proceed well (Table 1, entries 17−20). Trace or no desired product was observed in the absence of CuCl or $Ce(NO_3)_3$ (Table 1, entries 21−22). An investigation of the effect of solvent (Table 1, entries 16 and 23−25) revealed that use of CH_3CN greatly increased the yield of the reaction (90%, Table 1, entry 16). The role of CH_3CN in the reaction is not clear. CH_3CN is known to be a unique ligand in many useful copper transformations.[20] Replacement of ammonium chloride with other ammonia sources, including ammonium acetate, ammonium sulfate, and aqueous ammonia, resulted in slightly lower yields (Table 1, entries 26−28). In addition, the reaction failed to give the desired product when the procedure was carried out under a N_2 atmosphere.

Having the optimized reaction conditions in hand, we next explored the scope and generality of the condensation reaction using various (2-aminophenyl)methanols (**1**) and aldehydes (**2**) (Table 2). First, the reaction between (2-aminophenyl)-methanol (**1a**) and various benzaldehydes (**2b**−**2p**) was investigated under standard conditions. The results disclosed that the reactions proceeded smoothly and tolerated a wide range of functional groups, including methoxy, fluoro, chloro, bromo, formacyl, nitro, trifluoromethyl, thienyl, and furyl groups. When unsubstituted benzaldehyde (**2b**) was used as the substrate, the desired product 2-phenylquinazoline (**3b**) was isolated in excellent yield (Table 2, entry 2). The mono-substituent positions at the aryl moiety of aldehydes were evaluated, and the results demonstrated that steric effects of substituents had little effects on the reaction. For example, the reaction of **1a** with *p*- and *o*-methylbenzaldehyde resulted in the formation of the corresponding 2-*p*-tolylquinazoline (**3c**) and 2-*o*-tolylquinazoline (**3d**) in 86% and 83% yields, respectively (Table 2, entries 3 and 4). Moreover, a relatively large sterically hindered aldehyde, such as 2,6-dichlorobenzaldehyde (**2e**) could also be used as the substrate, affording the desired product **3e** in 84% yield (Table 2, entry 5). The electronic properties of the substituents on the phenyl ring of the aldehydes affected the yields of the reaction to some extent. In general, the aldehydes bearing an electron-withdrawing substituent (e.g., −Cl, −F, and −Br) (Table 2, entries 1, 9 and 10) produced a slightly higher yield of cyclization products than those analogues bearing an electron-donating substituent (e.g., −Me and −OR) (Table 2, entries 3 and 6−8). However, aldehydes bearing a strong electron-withdrawing substituent (e.g., $-CF_3$, CHO, and $-NO_2$) at the para position afforded slightly lower yields of products **3k**, **3l**, and **3m** (Table 2, entries 11−13). It is worth noting that 31% yield of additional product 2-(4-nitrophenyl)-4*H*-benzo[*d*]1,3-oxazine (**4m**) was isolated when 4-nitrobenzaldehyde (**2m**) was used as the substrate under standard conditions (Table 2, entry 13). Moderate yield of 2-(naphthalen-2-yl)quinazoline (**3n**) was observed when 1-naphthaldehyde (**2n**) was used as substrate (Table 2, entry 14). In addition, heterocyclic aldehydes, such as 2-furylaldehyde (**2o**) and 2-thienylaldehyde (**2p**) could also be used as substrates, leading to formation of the corresponding 2-(furan-2-yl)quinazoline (**3o**) and 2-(thiophen-2-yl)quinazoline (**3p**) in 91% and 93% yields, respectively (Table 2, entries 15 and 16). Notably, the chloro, fluoro, and bromo moieties

dx.doi.org/10.1021/jo401908g | J. Org. Chem. 2013, 78, 11342−11348

Table 1. Results of Screening for Optimal Conditions[a]



1a 2a 3a

entry	[Cu]	[Ce] + [NH_3] sources	base	solvent	yield[b] (%)
1	CuOTf	$(NH_4)_2Ce(NO_3)_6$	Li_2CO_3	CH_3CN	32[c]
2	CuOTf	$(NH_4)_2Ce(NO_3)_6$	K_2CO_3	CH_3CN	45[c]
3	CuOTf	$(NH_4)_2Ce(NO_3)_6$	KF	CH_3CN	17[c]
4	CuOTf	$(NH_4)_2Ce(NO_3)_6$	^tBuOK	CH_3CN	33[c]
5	CuOTf	$(NH_4)_2Ce(NO_3)_6$	K_3PO_4	CH_3CN	14[c]
6	CuOTf	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	60[c]
7	CuOAc	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	<5[c]
8	CuBr	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	58[c]
9	CuCl	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	71[c]
10	$CuCl_2$	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	44[c]
11	$CuBr_2$	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	38[c]
12	$CuSO_4$	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	41[c]
13	CuO	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	29[c]
14	$Cu(OTf)_2$	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	52[c]
15	$Cu(OAc)_2$	$(NH_4)_2Ce(NO_3)_6$	KOH	CH_3CN	46[c]
16	CuCl	$Ce(NO_3)_3{\cdot}6H_2O + NH_4Cl$	KOH	CH_3CN	90
17	CuCl	$CeCl_3{\cdot}7H_2O + NH_4Cl$	KOH	CH_3CN	53
18	CuCl	$CeF_3 + NH_4Cl$	KOH	CH_3CN	44
19	CuCl	$Ce(SO_4)_2{\cdot}4H_2O + NH_4Cl$	KOH	CH_3CN	67
20	CuCl	$Ce(OAc)_3{\cdot}xH_2O + NH_4Cl$	KOH	CH_3CN	69
21	CuCl	NH_4Cl[d]	KOH	CH_3CN	trace
22		$Ce(NO_3)_3{\cdot}6H_2O + NH_4Cl$	KOH	CH_3CN	0
23	CuCl	$Ce(NO_3)_3{\cdot}6H_2O + NH_4Cl$	KOH	PhCl	33
24	CuCl	$Ce(NO_3)_3{\cdot}6H_2O + NH_4Cl$	KOH	THF	42
25	CuCl	$Ce(NO_3)_3{\cdot}6H_2O + NH_4Cl$	KOH	toluene	12
26	CuCl	$Ce(NO_3)_3{\cdot}6H_2O + NH_4OAc$	KOH	CH_3CN	79
27	CuCl	$Ce(NO_3)_3{\cdot}6H_2O + (NH_4)_2SO_4$	KOH	CH_3CN	83
28	CuCl	$Ce(NO_3)_3{\cdot}6H_2O + NH_3{\cdot}H_2O$		CH_3CN	71

[a]Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol), **2a** (0.3 mmol), ammonia source (0.5 mmol), Cu source (20 mol %), bpy (10 mol %), TEMPO (10 mol %), base (2.5 equiv), Ce source (10 mol %), and solvent (2 mL), O_2, 30 °C, 24 h and then 80 °C for 24 h. [b]Isolated yield. [c]1.5 equiv of $(NH_4)_2Ce(NO_3)_6$ was used. [d]Without cerium salts.

(commonly used for cross-coupling reactions) in aldehydes were all tolerated and afforded a novel route to compounds **3a**, **3e**, **3i**, and **3j** in moderate and good yields, making further elaborations of the corresponding biaryl products possible (Table 2, entries 1, 5, 9, and 10). Moreover, terephthalaldehyde (**2l**), possessing the active formacyl group, was also tolerated well and afforded the corresponding 4-(quinazolin-2-yl)-benzaldehyde (**3l**) in 55% yield (Table 2, entry 12).

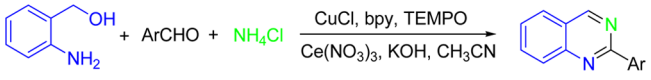
Next, we turned our attention to the effect of the reactions of various (2-aminophenyl)methanols **1b**−**1f** with benzaldehyde (**2b**) under standard conditions (Table 3). The electronic properties of groups on the phenyl ring moiety of (2-aminophenyl)methanols had some effects on the reaction. Both electron-donating (e.g., −Me) and electron-withdrawing (e.g., −F and −Cl) substituents were tolerated in the reaction. Generally, (2-aminophenyl)methanols having an electron-withdrawing substituent on the phenyl group gave a slightly higher yield of cyclization product. However, (2-aminoaryl)-methanols containing a strong electron-withdrawing group (e.g., $-NO_2$) on the benzene ring, such as 4-nitro-2-aminobenzyl alcohol (**2s**), led to the corresponding desired product **3s** in slightly lower yield. Steric effects of substituents had an obvious impact on the yield of the reaction. Substrate 5-methyl-2-aminobenzyl alcohol (**2t**) bearing a *p*-methyl group, for example, was treated with **1b** to afford 82% yield of **3t**, while the yield of **3u** was decreased to 65% from 3-methyl-2-aminobenzyl alcohol (**2u**) possessing an *o*-methyl group.

The present synthetic route to 2-arylquinazolines could be readily scaled up to gram quantity without difficulty. For instance, the reaction at the 20 mmol scale afforded the corresponding product 2-phenylquinazoline (**3a**) in 86% yield.

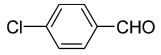
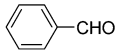
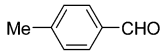
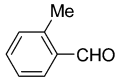
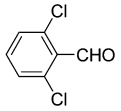
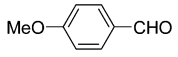
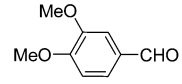
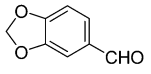
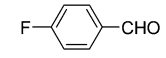
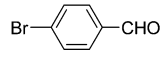
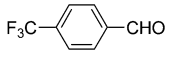
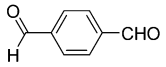
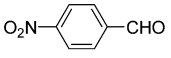
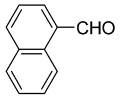
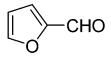
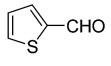
To elucidate the mechanism of formation of quinazolines, the following control experiments were performed under standard conditions as shown in Scheme 3. We found that 2-phenyl-4*H*-benzo[*d*]1,3-oxazine (**4b**) was obtained in 36% yield when the reaction of (2-aminophenyl)methanol (**1a**) with benzaldehyde was performed under standard conditions but in the absence of an ammonia source (Scheme 3a). However, the desired product **3b** could not be detected, and when 2-phenyl-4*H*-benzo[*d*]1,3-oxazine (**4b**) was treated with ammonium chloride under standard conditions, almost 90% of **4b** was recovered (Scheme 3b). On the other hand, a trace amount of benzonitrile was detected by GC/MS when benzaldehyde was treated with ammonium chloride under standard conditions (Scheme 3c). Thus, we next carried out the reaction between (2-aminophenyl)methanol (**1a**) and benzonitrile. However, the reaction failed to deliver the desired product **3b** under the same reaction conditions (Scheme 3d). 2-Aminobenzaldehyde was

dx.doi.org/10.1021/jo401908g | J. Org. Chem. 2013, 78, 11342−11348

Table 2. Substrate Scope of Aldehydes[a]



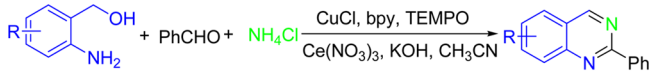
1a 2 3

Entry	ArCHO (2)		Product	Yield (%)[b]
1		**2a**	**3a**	90
2		**2b**	**3b**	93
3		**2c**	**3c**	86
4		**2d**	**3d**	83
5		**2e**	**3e**	84
6		**2f**	**3f**	81
7		**2g**	**3g**	73
8		**2h**	**3h**	76
9		**2i**	**3i**	97
10		**2j**	**3j**	87
11		**2k**	**3k**	72
12		**2l**	**3l**	55
13		**2m**	**3m**	56 (31)[c]
14		**2n**	**3n**	75
15		**2o**	**3o**	91
16		**2p**	**3p**	93

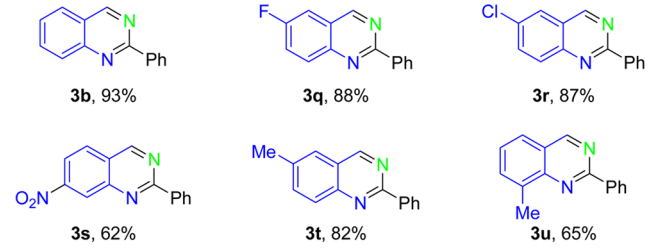
[a]Unless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol), **2** (0.3 mmol), NH_4Cl (0.5 mmol), CuCl (20 mol %), bpy (10 mol %), TEMPO (10 mol %), KOH (2.5 equiv), $Ce(NO_3)_3·6H_2O$ (10 mol %) and CH_3CN (2 mL), O_2, 30 °C, 24 h then 80 °C for 24 h. [b]Isolated yield. [c]31% yield of 2-(4-nitrophenyl)-4*H*-benzo[*d*]1,3-oxazine (**4m**) was isolated.

isolated in 87% yield, and 2-(aminomethyl)benzenamine was not detected by thin-layer cchromatography (TLC) or GC/MS analysis from the treatment of (2-aminophenyl)methanol (**1a**) with ammonium chloride under standard conditions (Scheme 3e). The desired product **3b** was isolated in 94% yield when 2-aminobenzaldehyde was used (Scheme 3f). These results revealed that that 2-aminobenzaldehyde is the key intermediate for the transformation.

Table 3. Substrate Scope of (2-Aminophenyl)methanols[a]

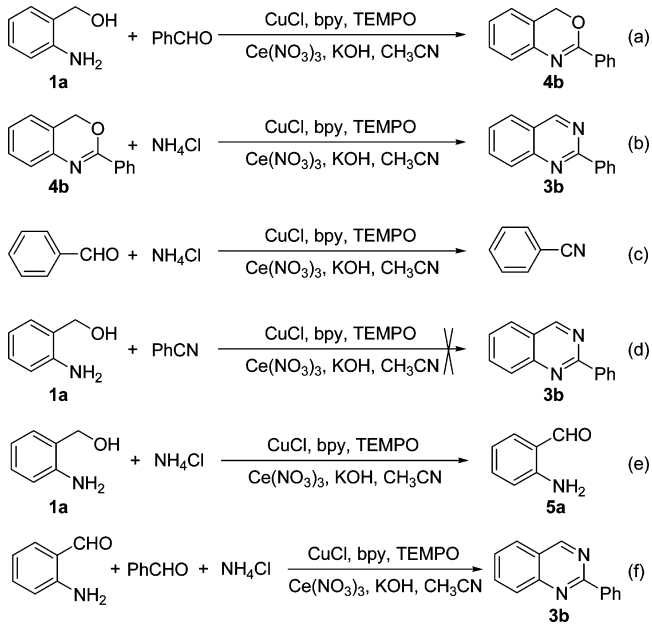


1b-1f 2b 3



[a]Reaction conditions: **1** (0.2 mmol), **2b** (0.3 mmol), NH_4Cl (0.5 mmol), CuCl (20 mol %), bpy (10 mol %), TEMPO (10 mol %), KOH (2.5 equiv), $Ce(NO_3)_3·6H_2O$ (10 mol %) and CH_3CN (2 mL), O_2, 30 °C, 24 h then 80 °C for 24 h; isolated yield.

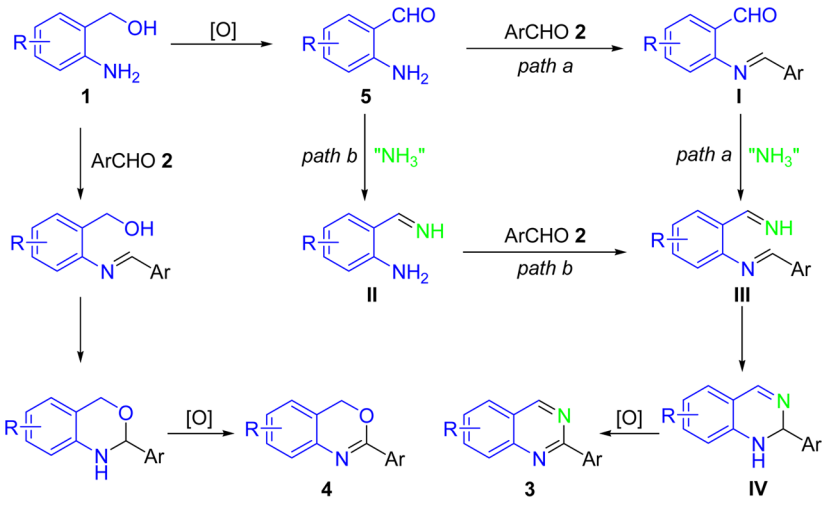
Scheme 3. Control Experiments



On the basis of the above experimental results and relevant reports in the literature, we proposed two possible reaction pathways for the formation of quinazolines (Scheme 4). The first step may involve the aerobic alcohol oxidation reaction of (2-aminophenyl)methanols **1** leading to 2-aminobenzaldehydes **5** by use of the CuCl/2,2′-bipyridine (bpy)/(2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) catalyst systems. In path a, intermediate **I** is formed from the reaction between the free NH_2 group of 2-aminobenzaldehydes **5** with aldehydes **2**. The formyl group of intermediate **I** can then react with the ammonia generated from ammonium chloride to give an imine **III**, which after cyclization generates dihydroquinazolines **IV**. Aromatization of **IV** yields quinazolines **3** as the desired products. In path b, 2-aminobenzaldehydes **5** can form intermediate **II** by reacting with ammonia generated from ammonium chloride. The free NH_2 group of intermediate **II**

dx.doi.org/10.1021/jo401908g | J. Org. Chem. 2013, 78, 11342−11348

Scheme 4. Plausible Reaction Pathways



can then react with the aldehyde to give an imine **III**, which, after simultaneous addition and cyclization reactions, affords the desired products **3**. It is worth mentioning that 2-aryl-4*H*-benzo[*d*]1,3-oxazines **4** are obtained when (2-aminophenyl)-methanols **1** are treated with aldehydes **2** in the absence of ammonia or with aldehydes bearing a strong electron-withdrawing substituent (e.g., $-NO_2$) even in the presence of ammonia. However, details of the mechanism of the formation of the quinazolines remain unclear at the current stage.

CONCLUSIONS

In summary, we have developed a new strategy for constructing 2-substituted quinazolines in moderate to excellent yields from the copper-catalyzed cascade reaction of (2-aminophenyl)-methanols, aldehydes, and ammonium chloride. Further efforts to extend this catalytic system to the preparation of other useful heterocyclic compounds are currently underway in our laboratories.

EXPERIMENTAL SECTION

General Information. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 or 300 MHz spectrometer (^{1}H at 500 or 300 MHz, ^{13}C at 125 or 75 MHz), with deuterated dimethyl sulfoxide (DMSO-d_6) or $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectra (HRMS) were recorded on an electrospray quadrupole time-of-flight (ESI-Q-TOF) mass spectrometer. Other commercially obtained reagents were used without further purification. All reactions were conducted by use of standard Schlenk techniques. Column chromatography was performed on EM silica gel 60 (300−400 mesh).

General Procedure for Copper-Catalyzed Synthesis of Quinazolines 3. To a Schlenk tube were added (2-aminophenyl)-methanols **1** (0.2 mmol), aldehyde **2a** (0.3 mmol), NH_4Cl (0.5 mmol), CuCl (20 mol %), bpy (10 mol %), TEMPO (10 mol %), KOH (2.5 equiv), $Ce(NO_3)_3{\cdot}6H_2O$ (10 mol %), and CH_3CN (2 mL). Next the tube was charged with O_2 (1 atm), and the mixture was was stirred constantly at 30 °C for 24 h and then at 80 °C for 24 h. After completion of the reaction, as monitored by TLC and GC/MS analysis, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with brine. After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired products **3**.

*2-(4-Chlorophenyl)quinazoline (**3a**).*[16a] R_f = 0.35 (hexane/ethyl acetate = 15:1), white solid (43.2 mg, 90% yield), mp 134−136 °C (lit. 133−135 °C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.72 (s, 1H), 8.57 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.0 Hz, 1H), 8.04−8.08 (m, 2H), 7.75−7.78 (m, 1H), 7.64 (d, J = 8.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 161.5, 158.8, 149.8, 136.3, 135.8, 135.1, 129.9, 128.9, 127.93, 127.90, 123.4. HRMS (ESI) m/z calcd for $C_{14}H_{10}ClN_2$ $[M + H]^+$ 241.0527, found 241.0538.

*2-Phenylquinazoline (**3b**).*[16a] R_f = 0.37 (hexane/ethyl acetate = 15:1), pale yellow solid (38.3 mg, 93% yield), mp 97−98 °C (lit. 97−98 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.70 (s, 1H), 8.55−8.59 (m, 2H), 8.17 (d, J = 8.1 Hz, 1H), 8.00−8.08 (m, 2H), 7.71−7.76 (m, 1H), 7.55−7.59 (m, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.3, 159.8, 149.8, 137.4, 134.8, 130.8, 128.7, 128.1, 127.9, 127.8, 123.3. HRMS (ESI) m/z calcd for $C_{14}H_{11}N_2$ $[M + H]^+$ 207.0917, found 207.0915.

*2-p-Tolylquinazoline (**3c**).*[16a] R_f = 0.44 (hexane/ethyl acetate = 10:1), yellow solid (37.8 mg, 86% yield), mp 108−109 °C (lit. 107−109 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.44 (s, 1H), 8.52 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 8.0 Hz, 1H), 7.87−7.90 (m, 2H), 7.56−7.60 (m, 1H), 7.35 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.1, 160.4, 150.8, 140.8, 135.3, 134.0, 129.4, 128.52, 128.50, 127.1, 127.0, 123.5, 21.5. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2$ $[M + H]^+$ 221.1073, found 221.1063.

*2-o-Tolylquinazoline (**3d**).*[21] R_f = 0.33 (hexane/ethyl acetate = 3:1), colorless oil (36.5 mg, 83% yield); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.49 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.89−7.95 (m, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.05−7.11 (m, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.4, 160.0, 157.7, 150.6, 134.0, 131.7, 130.8, 129.0, 128.5, 127.5, 127.0, 123.1, 120.7, 111.9, 56.0. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2$ $[M + H]^+$ 221.1073, found 221.1075.

*2-(2,6-Dichlorophenyl)quinazoline (**3e**).* R_f = 0.35 (hexane/ethyl acetate = 10:1), white solid (46.1 mg, 84% yield), mp 129−130 °C; IR (KBr) 2923, 2365, 1719, 1557, 1428, 1375, 182, 774, 718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.56 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.97−8.03 (m, 2H), 7.72−7.75 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.31−7.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.8, 160.3, 150.3, 137.8, 134.6, 134.2, 130.2, 128.6, 128.5, 128.1, 127.2, 123.6. HRMS (ESI) m/z calcd for $C_{14}H_9Cl_2N_2$ $[M + H]^+$ 275.0137, found 275.0150.

*2-(4-Methoxyphenyl)quinazoline (**3f**).*[16a] R_f = 0.33 (hexane/ethyl acetate = 10:1), white solid (38.2 mg, 81% yield), mp 92−93 °C (lit. 91−93 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.40 (s, 1H), 8.57−8.59 (m, 2H), 8.03 (d, J = 8.9 Hz, 1H), 7.86 (t, J = 9.7 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.9, 160.9, 160.4, 150.9, 134.0, 130.9 130.2, 128.4,

dx.doi.org/10.1021/jo401908g | J. Org. Chem. 2013, 78, 11342−11348

127.1, 126.8, 123.3, 114.0, 55.4. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$ 237.1022, found 237.1031.

2-(3,4-Dimethoxyphenyl)quinazoline (**3g**).[22] R_f = 0.41 (hexane/ethyl acetate = 5:1), white solid (38.8 mg, 73% yield), mp 110−111 °C (lit. 112−114 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.41 (s, 1H), 8.20 (d, J = 1.5 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.86−7.89 (m, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 4.06 (s, 3H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.7, 160.3, 151.4, 150.8, 149.1, 134.0, 130.9, 128.4, 127.1, 126.8, 123.3, 122.0, 111.2, 110.9, 56.0, 55.9. HRMS (ESI) m/z calcd for $C_{16}H_{15}N_2O_2$ $[M + H]^+$ 267.1128, found 267.1134.

2-(1,3-Dihydroisobenzofuran-5-yl)quinazoline (**3h**).[15b] R_f = 0.47 (hexane/ethyl acetate = 5:1), yellow solid (38 mg, 76% yield), mp 126−128 °C (lit. 123−125 °C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.63 (s, 1H), 8.12−8.19 (m, 2H), 7.99−8.00 (m, 3H), 7.68−7.71 (m, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.14 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.1, 159.3, 149.8, 149.7, 147.9, 134.7, 131.7, 127.74, 127.67, 127.3, 123.10, 123.07, 108.4, 107.6, 101.6. HRMS (ESI) m/z calcd for $C_{15}H_{11}N_2O_2$ $[M + H]^+$ 251.0815, found 251.0824.

2-(4-Fluorophenyl)quinazoline (**3i**).[16a] R_f = 0.3 (hexane/ethyl acetate = 20:1), white solid (43.5 mg, 97% yield), mp 135−137 °C (lit. 135−137 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.44 (s, 1H), 8.60−8.65 (m, 2H), 8.07 (d, J = 8.4 Hz, 1H), 7.91 (t, J = 7.8 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.7, 163.7, 160.5, 160.1, 150.7, 134.2, 130.7, 130.6, 128.6, 127.3, 127.1, 123.5, 115.6, 115.5. HRMS (ESI) m/z calcd for $C_{14}H_{10}FN_2$ $[M + H]^+$ 225.0823, found 225.0827.

2-(4-Bromophenyl)quinazoline (**3j**).[15c] R_f = 0.33 (hexane/ethyl acetate = 20:1), white solid (49.4 mg, 87% yield), mp 120−121 °C (lit. 120−121 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.43 (s, 1H), 8.50 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 9.0 Hz, 1H), 7.89−7.92 (m, 2H), 7.60−7.66 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.5, 160.1, 150.7, 137.0, 134.2, 131.8, 130.2, 128.6, 127.4, 127.1, 125.4, 123.6. HRMS (ESI) m/z calcd for $C_{14}H_{10}BrN_2$ $[M + H]^+$ 285.0022, found 285.0034.

2-[4-(Trifluoromethyl)phenyl]quinazoline (**3k**).[23] R_f = 0.43 (hexane/ethyl acetate = 5:1), white solid (39.5 mg, 72% yield), mp 143−144 °C (lit. not reported); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.76 (s, 1H), 8.75 (d, J = 8.5 Hz, 2H), 8.21 (d, J = 8.0 Hz, 1H), 8.06−8.12 (m, 2H), 7.93 (d, J = 8.5 Hz, 2H), 7.78−7.81 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 158.4, 149.7, 141.2, 135.1, 130.7, 150.5, 128.7, 128.4, 128.0, 127.9, 125.8, 125.7, 125.3, 123.6, 123.1. HRMS (ESI) m/z calcd for $C_{15}H_{10}F_3N_2$ $[M + H]^+$ 275.0791, found 275.0798.

4-(Quinazolin-2-yl)benzaldehyde (**3l**). R_f = 0.37 (hexane/ethyl acetate = 5:1), white solid (25.7 mg, 55% yield), mp 167−168 °C; IR (KBr): 2924, 2856, 2360, 1693, 1626, 1551, 1207, 1055, 796, 729, 688 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.12 (s, 1H), 9.76 (s, 1H), 8.75 (d, J = 8.0 Hz, 2H), 8.21 (d, J = 8.0 Hz, 1H), 8.07−8.10 (m, 4H), 7.78−7.81 (m,, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 193.0, 161.5, 158.7, 149.7, 142.6, 137.4, 135.1, 129.8, 128.6, 128.4, 128.0, 127.9, 123.5. HRMS (ESI) m/z calcd for $C_{15}H_{11}N_2O$ $[M + H]^+$ 235.0866, found 235.0879.

2-(4-Nitrophenyl)quinazoline (**3m**).[16b] R_f = 0.31 (hexane/ethyl acetate = 10:1), yellow solid (28.1 mg, 56% yield), mp 218−220 °C (lit. 218−219 °C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.80 (s, 1H), 8.80 (d, J = 9 Hz, 2H), 8.43 (d, J = 9.0 Hz, 2H), 8.24 (d, J = 9.0 Hz, 1H), 8.09−8.15 (m, 2H), 7.81−7.84 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.7, 157.9, 149.7, 148.8, 143.3, 135.3, 129.2, 128.7, 128.1, 128.0, 124.0, 123.6. HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3O_2$ $[M + H]^+$ 252.0768, found 252.0766.

2-(4-nitrophenyl)-4H-benzo[d]1,3-oxazine (**4m**).[16b] R_f = 0.34 (hexane/ethyl acetate = 10:1), white solid (15.8 mg, 31% yield), mp 93−94 °C (lit. 92−93 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.26−8.33 (m, 4H), 7.29−7.35 (m, 2H), 7.22−7.26 (m, 1H), 7.04 (d, J = 7.2 Hz, 1H), 5.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 149.6, 139.0, 138.3, 129.2, 128.8, 127.5, 125.2, 123.8, 123.4, 122.0, 66.7. HRMS (ESI) m/z calcd for $C_{14}H_{11}N_2O_3$ $[M + H]^+$ 255.0764, found 255.0763.

2-(Naphthalen-1-yl)quinazoline (**3n**).[21] R_f = 0.23 (hexane/ethyl acetate = 10:1), white solid (38.4 mg, 75% yield), mp 120−121 °C (lit. 120−121 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.60 (s, 1H), 8.70 (d, J = 8.0 Hz, 1H), 8.17−8.19 (m, 2H), 7.93−8.03 (m, 4H), 7.70 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.52−7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 160.4, 150.6, 136.3, 134.3, 134.2, 131.2, 130.4, 129.6, 128.7, 128.5, 127.7, 127.1, 126.8, 125.89, 125.87, 125.3, 123.1. HRMS (ESI) m/z calcd for $C_{18}H_{13}N_2$ $[M + H]^+$ 257.1073, found 257.1070.

2-(Furan-2-yl)quinazoline (**3o**).[16b] R_f = 0.3 (hexane/ethyl acetate = 10:1), brown solid (35.7 mg, 91% yield), mp 131−132 °C (lit. 131−132 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.38 (s, 1H), 8.09 (d, J = 9.0 Hz, 1H), 7.88−7.91 (m, 2 H), 7.69 (s, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 3.5 Hz, 1H), 6.61−6.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.7, 154.1, 152.5, 150.5, 145.3, 134.5, 128.4, 127.3, 123.4, 114.1, 112.3. HRMS (ESI) m/z calcd for $C_{12}H_9N_2O$ $[M + H]^+$ 197.0709, found 197.0708.

2-(Thiophen-2-yl)quinazoline (**3p**).[10a] R_f = 0.47 (hexane/ethyl acetate = 10:1), white solid (39.4 mg, 93% yield), mp 131−133 °C (lit. 132−134 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.35 (s, 1H), 8.14−8.16 (m, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.85−7.90 (m, 2H), 7.51−7.59 (m, 2H), 7.18−7.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.5, 157.9, 150.7, 143.9, 134.3, 129.9, 129.2, 128.3, 128.2, 127.2, 127.0, 123.4. HRMS (ESI) m/z calcd for $C_{12}H_9N_2S$ $[M + H]^+$ 213.0481, found 213.0487.

6-Fluoro-2-phenylquinazoline (**3q**).[14] R_f = 0.27 (hexane/ethyl acetate = 10:1), white solid (39.4 mg, 88% yield), mp 120−121 °C (lit. 120−121 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.41 (s, 1H), 8.58−8.60 (m, 2H), 8.07−8.12 (m, 1H), 7.64−7.69 (m, 1H), 7.52−7.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.4, 160.7, 159.8, 159.7, 159.4, 148.0, 137.7, 131.4, 131.3, 130.7, 128.6, 128.5, 124.6, 124.4, 124.0, 123.9, 110.2, 110.0. HRMS (ESI) m/z calcd for $C_{14}H_{10}FN_2$ $[M + H]^+$ 225.0823, found 225.0827.

6-Chloro-2-phenylquinazoline (**3r**).[12c] R_f = 0.39 (hexane/ethyl acetate = 20:1), pale yellow solid (41.8 mg, 87% yield), mp 157−159 °C (lit. 157−159 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.40 (s, 1H), 8.58−8.62 (m, 2H), 8.03 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.82−7.85 (m, 1H), 7.52−7.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.4, 159.5, 149.3, 137.6, 135.1, 132.8, 130.9, 130.4, 128.7, 128.6, 125.8, 124.0. HRMS (ESI) m/z calcd for $C_{14}H_{10}ClN_2$ $[M + H]^+$ 241.0527, found 241.0535.

7-Nitro-2-phenylquinazoline (**3s**). R_f = 0.28 (hexane/ethyl acetate = 10:1), white solid (31.1 mg, 62% yield), mp 140−143 °C; IR (KBr) 2925, 1687, 1567, 1526, 1421, 1326, 1291, 927, 823, 740, 706, 686, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.61 (s, 1H), 8.96 (s, 1H), 8.65−8.66 (m, 2H), 8.36−8.37 (m, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.56−7.57 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 160.8, 151.2, 150.5, 136.9, 131.6, 129.0, 128.9, 128.8, 125.7, 124.9, 120.7. HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3O_2$ $[M + H]^+$ 252.0768, found 252.0772.

6-Methyl-2-phenylquinazoline (**3t**).[24] R_f = 0.41 (hexane/ethyl acetate = 10:1), pale yellow solid (36.1 mg, 82% yield), mp 130−132 °C (lit. 130−132 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.38 (s, 1H), 8.60 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 8.5 Hz, 1H), 7.72−7.74 (m, 1H), 7.67 (s, 1H), 7.50−7.55 (m, 3H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.4, 159.7, 149.4, 138.2, 137.4, 136.4, 130.4, 128.6, 128.4, 128.3, 125.8, 123.6, 21.6. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2$ $[M + H]^+$ 221.1073, found 221.1068.

8-Methyl-2-Phenylquinazoline (**3u**).[25] R_f = 0.32 (hexane/ethyl acetate = 20:1), pale yellow solid (28.6 mg, 65% yield), mp 59−61 °C (lit. 59−61 °C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.64 (s, 1H), 8.60 (m, 2H), 7.96 (d, J = 8 Hz, 1H), 7.86 (d, J = 7 Hz, 1H), 7.75−7.62 (m, 4H), 2.78 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.3, 158.9, 148.7, 137.7, 135.9, 134.3, 130.7, 128.7, 128.1, 127.3, 125.4, 123.2, 16.4. HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2$ $[M + H]^+$ 221.1073, found 221.1076.

2-Aminobenzaldehyde (**5a**).[26] R_f = 0.24 (hexane/ethyl acetate = 10:1), colorless oil (21.1 mg, 87% yield); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.87 (s, 1H), 7.47−7.49 (m, 1H), 7.29−7.33 (m, 1H), 6.73−6.76 (m, 1H), 6.65 (d, J = 8.5 Hz, 1H), 6.12 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.0, 149.8, 135.7, 135.1, 118.8, 116.3, 116.0.

dx.doi.org/10.1021/jo401908g | J. Org. Chem. 2013, 78, 11342−11348

HRMS (ESI) m/z calcd for C_7H_8NO $[M + H]^+$ 122.0600, found 122.0598.

*2-Phenyl-4H-benzo[d]1,3-oxazine (**4b**).*[16b] R_f = 0.26 (hexane/ethyl acetate = 15:1), white solid (15.1 mg, 36% yield), mp 91−92 °C (lit.[1] 92−93 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13−8.15 (m, 1H), 7.41−7.50 (m, 3H), 7.28−7.32 (m, 2H), 7.16−7.21 (m, 1H), 7.03 (d, J = 87.5 Hz, 1H), 5.40 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7, 139.7, 132.4, 131.4, 129.0, 128.2, 128.0, 126.4, 124.7, 123.7, 122.3, 66.4. HRMS (ESI) m/z calcd for $C_{14}H_{12}NO$ $[M + H]^+$ 210.0913, found 210.0912.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail jiuxichen@wzu.edu.cn.

*E-mail huayuewu@wuz.edu.cn; fax 86-577-8836-8280.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21102105 and 21272176) and Natural Science Foundation of Zhejiang Province (LY12B02011) for financial support.

■ REFERENCES

(1) (a) Xiao, X.; Antony, S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2006**, *49*, 1408. (b) Cinelli, M. A.; Morrell, A.; Dexheimer, T. S.; Scher, E. S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2008**, *51*, 4609. (c) Oh, S.; Park, S. B. *Chem. Commun.* **2011**, *47*, 12754.

(2) (a) Antonello, A.; Hrelia, P.; Leonardi, A.; Marucci, G.; Rosini, M.; Tarozzi, A.; Tumiatti, V.; Melchiorre, C. *J. Med. Chem.* **2005**, *48*, 28. (b) Rosini, M.; Antonello, A.; Cavalli, A.; Bolognesi, M. L.; Minarini, A.; Marucci, G.; Poggesi, E.; Leonardi, A.; Melchiorre, C. *J. Med. Chem.* **2003**, *46*, 4895. (c) Wilson, L. J. *Org. Lett.* **2001**, *3*, 585.

(3) (a) Oude Munnink, T. H.; de Vries, E. G. E.; Vedelaar, S. R.; Timmer-Bosscha, H.; Schröder, C. P.; Brouwers, A. H.; Lub-de Hooge, M. N. *Mol. Pharmaceutics* **2012**, *9*, 2995. (b) Mahboobi, S.; Sellmer, A.; Winkler, M.; Eichhorn, E.; Pongratz, H.; Ciossek, T.; Baer, T.; Maier, T.; Beckers, T. *J. Med. Chem.* **2010**, *53*, 8546.

(4) Hu, S.-J.; Long, W.; Wang, F.; Li, Z.-Q. World Patent WO 064 128, 2013.

(5) Henderson, E. A.; Bavetsias, V.; Theti, D. S.; Wilson, S. C.; Clauss, R.; Jackman, A. L. *Bioorg. Med. Chem.* **2006**, *14*, 5020.

(6) (a) Chien, T.-C.; Chen, C.-S.; Yu, F.-H.; Chern, J.-W. *Chem. Pharm. Bull.* **2004**, *52*, 1422. (b) Herget, T.; Freitag, M.; Morbitzer, M.; Kupfer, R.; Stamminger, T.; Marschall, M. *Antimicrob. Agents Chemother.* **2004**, *48*, 4154.

(7) Waisser, K.; Gregor, J.; Dostal, H.; Kunes, J.; Kubicova, L.; Klimesova, V.; Kaustova, J. *Farmaco* **2001**, *56*, 803.

(8) Madapa, S.; Tusi, Z.; Mishra, A.; Srivastava, K.; Pandey, S. K.; Tripathi, R.; Puri, S. K.; Batra, S. *Bioorg. Med. Chem.* **2009**, *17*, 222.

(9) Li, W.-W.; Wang, X.-Y.; Zheng, R.-L.; Yan, H.-X.; Cao, Z.-X.; Zhong, L.; Wang, Z.-R.; Ji, P.; Yang, L.-L.; Wang, L.-J.; Xu, Y.; Liu, J.-J.; Yang, J.; Zhang, C.-H.; Ma, S.; Feng, S.; Sun, Q.-Z.; Wei, Y.-Q.; Yang, S.-Y. *J. Med. Chem.* **2012**, *55*, 3852.

(10) (a) Wang, C.; Li, S.; Liu, H.; Jiang, Y.; Fu, H. *J. Org. Chem.* **2010**, *75*, 7936. (b) Huang, C.; Fu, Y.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Chem. Commun.* **2008**, 6333.

(11) (a) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem.* **2009**, *74*, 4934. (b) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *Chem. Commun.* **2008**, 2935.

(12) (a) Han, B.; Wang, C.; Han, R. F.; Yu, W.; Duan, X. Y.; Fang, R.; Yang, X. L. *Chem. Commun.* **2011**, *47*, 7818. (b) Karnakar, K.; Shankar, J.; Murthy, S. N.; Ramesh, K.; Nageswar, Y. V. D. *Synlett* **2011**, 1089. (c) Zhang, J. T.; Zhu, D. P.; Yu, C. M.; Wan, C. F.; Wang, Z. Y. *Org. Lett.* **2010**, *12*, 2841. (d) Zhang, J. T.; Yu, C. M.; Wang, S. J.; Wan, C. F.; Wang, Z. Y. *Chem. Commun.* **2010**, *46*, 5244.

(13) (a) Zhang, Z.-H.; Zhang, X.-N.; Mo, L.-P.; Li, Y.-X.; Ma, F.-P. *Green Chem.* **2012**, *14*, 1502. (b) Panja, S. K.; Dwivedi, N.; Saha, S. *Tetrahedron Lett.* **2012**, *53*, 6167.

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

(15) (a) Vanden Eynde, J. J.; Godin, J.; Mayence, A.; Maquestiau, A.; Anders, E. *Synthesis* **1993**, 867. (b) Peng, Y.; Zeng, Y.; Qiu, G.; Cai, L.; Pike, V. W. *J. Heterocycl. Chem.* **2010**, *47*, 1240. (c) Maheswari, C. U.; Kumar, G. S.; Venkateshwar, M.; Kumar, R. A.; Kantam, M. L.; Reddy, K. R. *Adv. Synth. Catal.* **2010**, *352*, 341.

(16) (a) Han, B.; Yang, X.-L.; Wang, C.; Bai, Y.-W.; Pan, T.-C.; Chen, X.; Yu, W. *J. Org. Chem.* **2012**, *77*, 1136. (b) Fang, J.; Zhou, J.; Fang, Z. *RSC Adv.* **2013**, *3*, 334.

(17) Verma, A. K.; Choudhary, D.; Saunthwal, R. K.; Rustagi, V.; Patel, M.; Tiwari, R. K. *J. Org. Chem.* **2013**, *78*, 6657.

(18) Selected examples for the copper-catalyzed organic reaction: (a) Zhang, J.; Chen, J.; Liu, M.; Zheng, X.; Ding, J.; Wu, H. *Green Chem.* **2012**, *14*, 912. (b) Chen, J.; Wang, X.; Zheng, X.; Ding, J.; Liu, M.; Wu, H. *Tetrahedron* **2012**, *68*, 8905. (c) Zheng, H.; Ding, J.; Chen, J.; Liu, M.; Gao, W.; Wu, H. *Synlett* **2011**, 1626. (d) Zheng, H.; Zhang, Q.; Chen, J.; Liu, M.; Cheng, S.; Ding, J.; Wu, H.; Su, W. *J. Org. Chem.* **2009**, *74*, 943.

(19) (a) Chen, J.; Su, W.; Wu, H.; Liu, M.; Jin, C. *Green Chem.* **2007**, *9*, 972. (b) Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 3814.

(20) Rach, S. F.; Kuhn, F. E. *Chem. Rev.* **2009**, *109*, 2061.

(21) Yuan, H.; Yoo, W.-J.; Miyamura, H.; Kobayashi, S. *Adv. Synth. Catal.* **2012**, *354*, 2899.

(22) Vypolzov, A. V.; Darin, D. V.; Ryazanov, S. G.; Lobanov, P. S. *Chem. Heterocycl. Compd.* **2011**, *46*, 1481.

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

(24) Rossi, E.; Elisabetta, R. *Synthesis* **1989**, 214.

(25) Wang, Y.; Chen, H.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 11980.

(26) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901.