Organic LETTERS

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A Novel Ruthenium-Catalyzed Dehydrogenative Synthesis of 2-Arylquinazolines from 2-Aminoaryl Methanols and Benzonitriles

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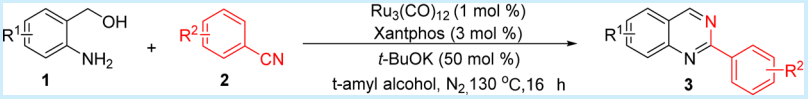
Supporting Information

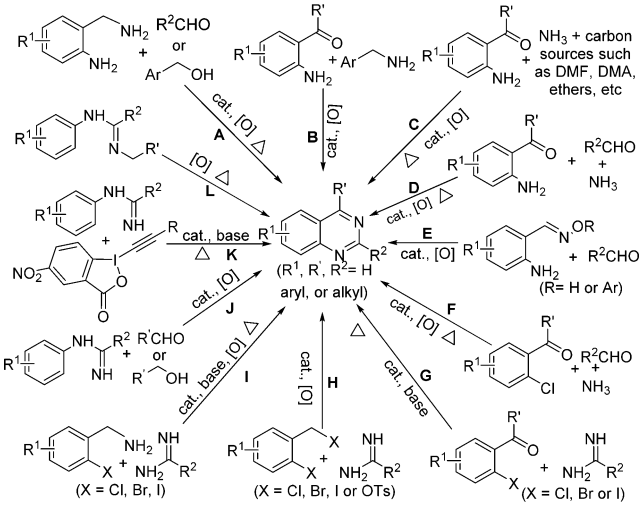


ABSTRACT: By employing a commercially available $Ru_3(CO)_{12}$/Xantphos/*t*-BuOK catalyst system, a novel and straightforward ruthenium-catalyzed dehydrogenative synthesis of 2-arylquinazolines has been demonstrated. A series of 2-aminoaryl methanols were efficiently converted in combination with different types of benzonitriles into various desired products in moderate to good yields upon isolation. The synthetic protocol proceeds with the advantages of operational simplicity, high atom efficiency, broad substrate scope, and no need for the use of less environmentally benign halogenated reagents, offering an important basis for accessing 2-arylquinazolines.

The quinazoline moiety is the core structure of numerous alkaloids and functional molecules that exhibit diverse biological and therapeutic activities such as antibacterial,[1] antiviral,[2] anticonvulsant,[3] and anticancer[4] and are potent inhibitors of the epidermal growth factor receptors of tyrosine kinase.[5] For example, erlotinib and gefitinib are well-known drugs used for the treatment of lung cancer. Moreover, quinazolines could serve as valuable intermediates for various synthetic purposes including the preparation of functionalized materials.[6]

The first example for the synthesis of quinazolines was reported by Griess in 1869 through the reaction of cyanogen with anthranilic acid. Due to the increasing importance of quinazoline derivatives, much attention has been focused on the development of alternative approaches for accessing this type of compound in the past decade, which mainly involve (1) oxidative condensation of 2-aminobenzylamine with benzaldehydes or benzyl alcohols (Scheme 1, approach A),[7] *o*-carbonyl anilines with benzyl amines (approach B),[8a,b] or ammonia and different carbon sources[8c−e] (approaches C and D); (2) condensation of oxime derivatives with aldehydes (approach E);[9] (3) oxidative coupling of *o*-carbonyl halobenzenes with ammonia and aldehydes (approach F);[10] (4) Ullmann or Buchwald−Hartwig amination-involved cyclization of amidines with *o*-carbonyl halobenzenes[11a] (approach G), 2-halobenzyl halides[11b] or 2-halobenzyl tosylates (approach H),[11c] and 2-halobenzyl amines (approach I);[11d] (5) oxidative coupling of amidines with benzyl alcohols or bezaldehyes (approach J)[11e] and hypervalent iodine-substituted alkynes (approach K);[11f] and (6) intramolecular oxidative cyclization of N-alkylated arylamidines (approach L).[12] Despite these contributions, many of them require the addition of excess oxidants and the use of special prefunctionalized or less environmentally benign halogenated reagents, which could result in preparation difficulties or a detrimental influence on the environment. From the viewpoint of green synthesis concerns, development of environmentally friendly shortcuts for accessing quinazolines from stable and easily available substrates still remains a demanding goal.

Scheme 1. Representative Methods for Accessing Quinazolines



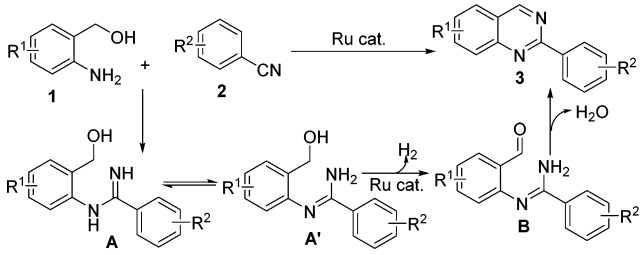
Upon a thorough literature investigation, it is understandable that the synthesis of quinazolines from 2-aminobenzaldehydes and benzonitriles is less likely due to the 2-aminobenzaldehydes tending to undergo a homocondensation. Inspired by our recent work on ruthenium-catalyzed transformation of abundant and sustainable alcohols into value-added products,[13]

Received: October 18, 2014

   dx.doi.org/10.1021/ol503052s | *Org. Lett.* XXXX, XXX, XXX−XXX

we believe such a synthetic goal could be realized by replacing 2-aminobenzaldehydes with 2-aminobenzyl alcohols **1** in the presence of a suitable ruthenium catalyst system. Through an acceptorless dehydrogenative coupling process,[14] the reaction might undergo the following tandem sequences: (1) The nucleophilic addition of the amino group of **1** to the benzonitrile **2** forms an amidine intermediate **A**. (2) Then, the ruthenium-catalyzed dehydrogenation of the alcohol unit of **A** gives an *o*-carbonyl amidine **B**. (3) Finally, the thermodynamically favorable intramolecular condensation of **B** would afford the desired quinazoline product **3** (Scheme 2).

Scheme 2. Possible Pathway for Accessing Quinazolines



With the above-described idea in mind, we initiated our investigations by choosing the synthesis of 2-phenylquinazoline **3a** from (2-aminophenyl)methanol **1a** and benzonitrile **2a** as a model reaction to determine an efficient reaction system. First, five ruthenium catalysts were tested by performing the reaction at 130 °C for 16 h using *t*-BuOK as the base, Xantphos (**L1**) as a ligand in *t*-amyl alcohol (Figure 1; see **cat. 1**−**cat. 5** and **L1**).

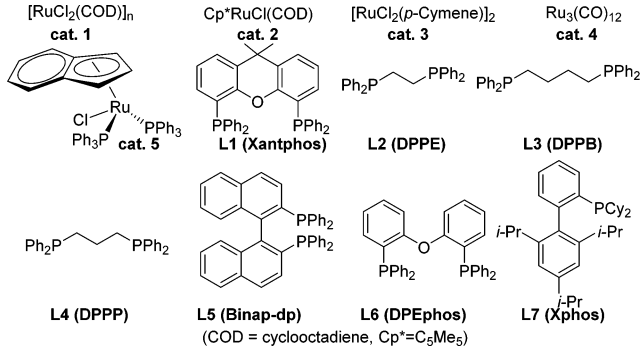
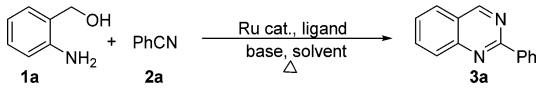


Figure 1. Catalysts and ligands tested for the optimization of reaction conditions.

$Ru_3(CO)_{12}$ (**cat. 4**) exhibited the highest activity in the formation of product **3a** along with a small portion of **1a** decomposing to aniline (Table 1, entries 1−5). The absence of catalyst failed to give any desired product (Table 1, entry 6). Then, **cat. 4** in combination with the other six diphosphine ligands was tested, and the results show that these ligands were less effective than Xantphos (Figure 1 **L2**−**L7** and Table 1, entries 7−12). Further, several other bases were proven to be totally ineffective or inferior to *t*-BuOK (Table 1, entries 13 and 14). Hence, we chose **cat. 4**/**L1**/*t*-BuOK as the preferred combination. An increase of base loading resulted in an improved yield, and 50 mol % was sufficient to result in a desirable yield (Table 1, entry 15). However, both increase and decrease of reaction temperature could not afford an improved yield (Table 1, entry 16). Finally, the reaction under air atmosphere failed to give

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	base	3a, yield %[b]
1	**cat. 1**	**L1**	*t*-BuOK	38
2	**cat. 2**	**L1**	*t*-BuOK	trace
3	**cat. 3**	**L1**	*t*-BuOK	40
4	**cat. 4**	**L1**	*t*-BuOK	53
5	**cat. 5**	**L1**	*t*-BuOK	48
6		**L1**	*t*-BuOK	
7	**cat. 4**	**L2**	*t*-BuOK	31
8	**cat. 4**	**L3**	*t*-BuOK	trace
9	**cat. 4**	**L4**	*t*-BuOK	34
10	**cat. 4**	**L5**	*t*-BuOK	20
11	**cat. 4**	**L6**	*t*-BuOK	15
12	**cat. 4**	**L7**	*t*-BuOK	10
13	**cat. 4**	**L1**	K_2CO_3, Cs_2CO_3 or NaOMe	trace
14	**cat. 4**	**L1**	CsOH	50
15	**cat. 4**	**L1**	*t*-BuOK	78[c]
16	**cat. 4**	**L1**	*t*-BuOK	78,[d] 69[e]
17	**cat. 4**	**L1**	*t*-BuOK	*f*

[a]Unless otherwise stated, all reactions were carried out under nitrogen atmosphere by using **1a** (0.5 mmol), **2a** (0.7 mmol), catalyst (**cat. 1**, **cat. 2**, and **cat. 5**: 3 mol %; **cat. 3**: 1.5 mol %; **cat. 4**: 1 mol %), ligand (3 mol %), base (20 mol %), *t*-amyl alcohol (1.5 mL), temperature (130 °C), reaction time (16 h). [b]GC yield using hexadecane as an internal standard. [c]Base loading: 50 or 60 mol %. [d]140 °C. [e]120 °C. [f]Under air atmosphere.

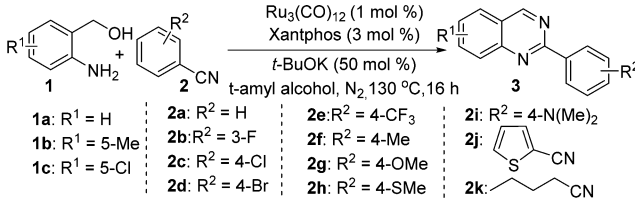
even a trace of desired product (Table 1, entry 17). Hence, the optimal reaction condition is indicated in entry 15 of Table 1.

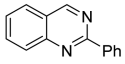
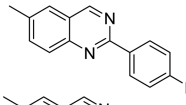
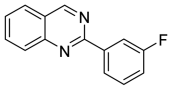
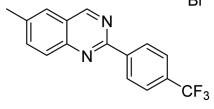
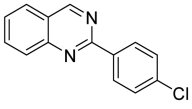
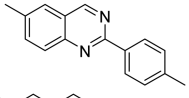
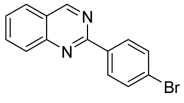
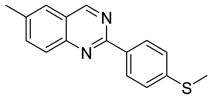
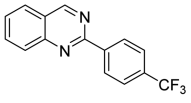
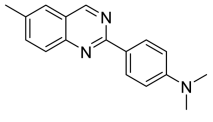
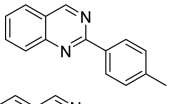
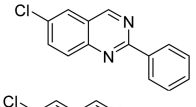
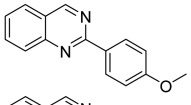
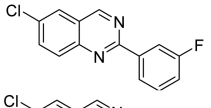
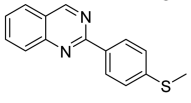
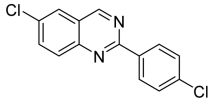
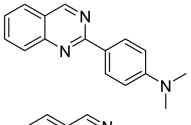
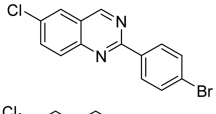
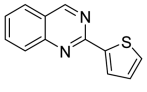
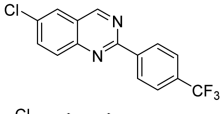
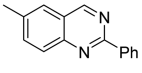
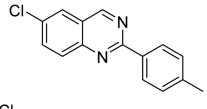
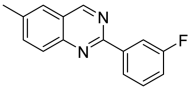
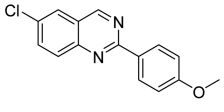
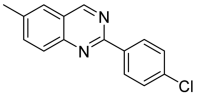
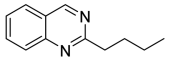
With the optimal reaction conditions in hand, we examined the generality and the limitations of the synthetic protocol. The reactions of **1a** in combination with a variety of benzonitriles, including the heteroaryl **2j**, were tested. As shown in Table 2, all the reactions proceeded smoothly and furnished the desired products in moderate to good yields upon isolation (Table 2, entries 1−10). It was found that the substituents on the aryl ring of the benzonitriles have a certain influence on the formation of products. Specifically, the nitriles bearing an electron-withdrawing group (i.e., F−, Cl−, Br−, and $-CF_3$) (Scheme 2, **3b**−**3e**) afforded the products in relatively higher yields than the electron-rich ones (i.e., −Me, −OMe, −SMe, and $-N(Me)_2$) (Scheme 2, **3f**−**3i**); this phenomenon can be rationalized as the electron-deficient benzonitriles benefit from the nucleophilic addition of the amino group of **1a** to the cyano center, which is in agreement with the possible mechanism proposed in Scheme 1.

To further explore the substrate scope, we next turned our attention to examine the reactions of different substituted 2-aminoaryl alcohols with various benzonitriles. Gratifyingly, all the substrates underwent efficient cyclization to afford the desired products in moderate to good isolated yields (Table 2, entries 11−25). Except for the substituent influence of benzonitriles, it was found that the electron-donating group containing 2-aminoaryl methanol **1b** afforded the desired product in higher yields (Table 2, entries 11−16) than the relatively electron-poor **1c** (Table 2, entries 19−25), which can be ascribed to the electron-rich substituents that could enhance the nucleophilicity of the amino group of **1b**, thus favoring the nucleophilic addition to the benzonitriles. Moreover, the reaction of **1a** with pentanenitrile **2k** led to an inseparable

dx.doi.org/10.1021/ol503052s | *Org. Lett.* XXXX, XXX, XXX−XXX

Table 2. Convenient Synthesis of 2-Arylquinazolines[a]



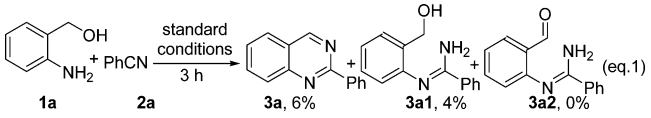
entry	1	2	product structure	yield% of 3[b]	entry	1	2	product structure	yield% of 3[b]
1	**1a**	**2a**		**3a**: 63	14	**1b**	**2d**		**3n**, 70
2	**1a**	**2b**		**3b**, 66	15	**1b**	**2e**		**3o**, 65
3	**1a**	**2c**		**3c**, 76	16	**1b**	**2f**		**3p**, 71
4	**1a**	**2d**		**3d**, 72	17	**1b**	**2h**		**3q**, 53
5	**1a**	**2e**		**3e**, 70	18	**1b**	**2i**		**3r**, 50
6	**1a**	**2f**		**3f**, 53	19	**1c**	**2a**		**3s**, 50
7	**1a**	**2g**		**3g**, 55	20	**1c**	**2b**		**3t**, 62
8	**1a**	**2h**		**3h**, 58	21	**1c**	**2c**		**3u**, 60
9	**1a**	**2i**		**3i**, 53	22	**1c**	**2d**		**3v**, 61
10	**1a**	**2j**		**3j**, 56	23	**1c**	**2e**		**3w**, 51
11	**1b**	**2a**		**3k**, 63	24	**1c**	**2f**		**3x**, 50
12	**1b**	**2b**		**3l**, 67	25	**1c**	**2g**		**3y**, 43
13	**1b**	**2c**		**3m**, 73	26	**1a**	**2k**		**3z**, 18[c]

[a]Unless otherwise stated, all reactions were carried out under nitrogen atmosphere by using **1a** (0.5 mmol), **2a** (0.7 mmol), catalyst (1 mol %), ligand (3 mol %), base (50 mol %), *t*-amyl alcohol (1.5 mL), temperature (130 °C), reaction time (16 h). [b]Isolated yield. [c]GC yield.

mixture, and the expected product 2-alkylquinazoline **3z** was detected in 18% GC yield (Table 2, entry 26). Noteworthy, all the obtained products possess a nonsubstituted C−H unit at position 4, which offers a potential for further elaboration of complex molecules via direct C−H bond functionalization.[15] Moreover, because the aryl groups are *ortho* to the nitrogen atom, the products have the potential to be utilized as the C∧N ligands for the preparation of organometallic complexes or materials.[16]

To gain insight into the possible information on the quinazoline forming process, the reaction of **1a** and **2a** was interrupted after 3 h to analyze the reaction intermediates (eq 1). Except for the generation of product **3a** and amidine **3a1** in 6 and

dx.doi.org/10.1021/ol503052s | *Org. Lett.* XXXX, XXX, XXX−XXX



4% yields, respectively, we did not observe any carbonyl intermediate **3a2**, indicating that the addition of the amino group of **1a** to the benzonitrile **2a** as well as the intramolecular imination steps are faster than the alcohol dehydrogenation process. Thus, the alcohol oxidation is believed to be a rate-determining step in the whole annulation process.

In summary, we have developed a novel method for the convenient synthesis of 2-arylquinazolines. By employing a commercially available $Ru_3(CO)_{12}$/Xantphos/*t*-BuOK catalyst system, a series of 2-aminoaryl methanols were efficiently converted in combination with a different type of benzonitriles into various desired products in moderate to good yields upon isolation. The synthetic protocol proceeds with the advantages of operational simplicity, high atom efficiency, broad substrate scope, and no need for the use of less environmentally benign halogenated reagents, offering an important basis for accessing 2-arylquinazolines. Considering the importance of 2-arylquinazolines in biological, medicinal, and synthetic organic chemistry, the presented method has the potential to be frequently employed for various applications. Further studies utilizing this synthetic protocol for the construction of position-4-substituted quinazolines are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to the funds of the National Natural Science Foundation of China (21472052 and 21101080), Fundamental Research Funds for the Central Universities of China (2014ZZ0047), and Distinguished talent program of SCUT.

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dx.doi.org/10.1021/ol503052s | *Org. Lett.* XXXX, XXX, XXX−XXX