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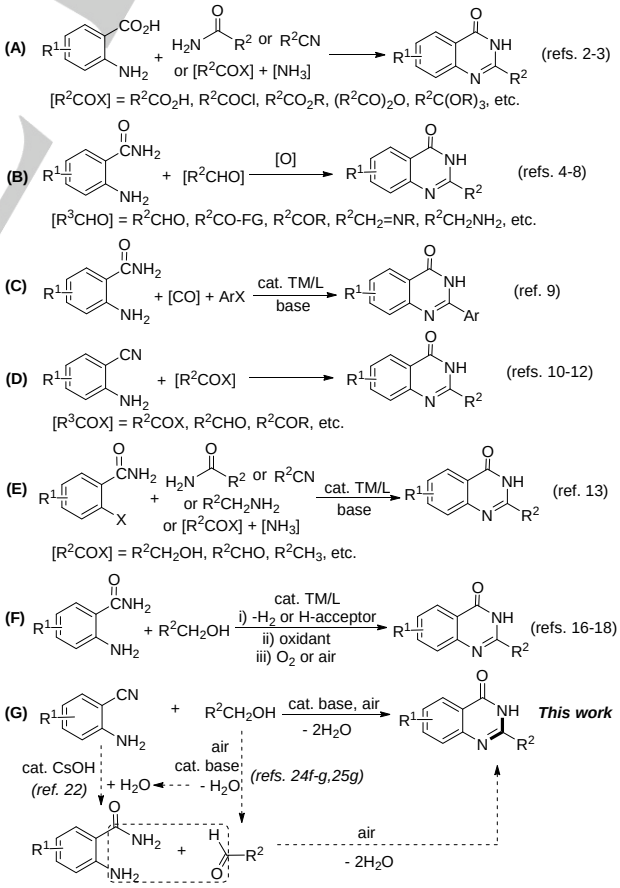
Efficient Synthesis of Quinazolinones by Transition Metal-Free Direct Aerobic Oxidative Cascade Annulation of Alcohols with *o*-Aminoarylnitriles

Qi Wang,[a] Miao Lv,[a] Jianping Liu,[b] Yang Li,[b] Hongen Cao,*[a] Xu Zhang,[a] and Qing Xu*[a,b]

Abstract: A mild and atom-economic method is developed for direct and efficient synthesis of quinazolinones via a transition metal-free aerobic oxidative cascade annulation reaction of the widely available *o*-aminoarylnitriles and alcohols. Air can be employed as an effective oxidant under mild conditions, generating water as the only byproduct. Possibly owing to the "cesium effect", the water soluble CsOH is the best base as it's found crucial in all the key steps of the reaction mechanism. Since a wide range of substrates can be used to prepare substituted quinazolinones without contamination by transition metal residues, this method may be of potential applications in pharmaceutical synthesis. Possible reaction paths were also proposed according to the control reactions.

Heterocycle derivatives have broad utilities in many fields especially the organic, pharmaceutical, and natural product synthesis, agrochemistry, materials and life science. For example, quinazolinone motif and derivatives are abundant in numerous synthetic compounds and natural alkaloids having diverse biological and pharmacological activities such as antimalarial, antimicrobial, anti-inflammatory, anticonvulsant, antihypertensive, anti-diabetic, anticancer, antitumor, cholinesterase inhibitory, dihydrofolate reductase inhibitory, and kinase inhibitory properties.[1,2] Hence, a variety of methods have been developed for quinazolinone skeleton construction.[2-19] Among the methods reported, annulation reactions of *o*-aminoaryl acids and derivatives may be the most employed strategies, which include the condensation of *o*-aminoaryl acids with amides, nitriles, or acid derivatives plus a nitrogen source (Scheme 1A),[2,3] the dehydrogenative or oxidative annulation of *o*-aminoarylamides with aldehydes,[4] masked aldehydes,[5] ketones,[6] imines,[7] or amines[8] (Scheme 1B), the carbonylative annulation of *o*-aminoarylamides with a CO source and aryl halides (Scheme 1C),[9] and annulation of *o*-aminoarylnitriles with acid derivatives,[10] aldehydes,[11] or ketones[12] (Scheme 1D). Moreover, transition metal-catalyzed coupling reactions of *o*-haloarylamides with amides, nitriles, amines, or aldehyde equivalents plus a nitrogen source (Scheme 1E)[13] as well as other annulation reactions[2,14] have also received much attention recently. Meanwhile, since alcohols are known as a class of greener, more available, more economic, more stable, and less toxic chemicals,[15] using alcohols instead of the above mentioned aldehydes, aldehyde equivalents, or acid derivatives in annulation reactions of *o*-aminoarylamides through transition metal-catalyzed dehydrogenative,[16] oxidative,[17] or aerobic oxidative[18] strategies (Scheme 1F) have also aroused much interest in recent years. Similarly, the reactions of alcohols with *o*-nitroarylamides[19] or *o*-nitroarylnitriles[20] were also described recently. Although various quinazolinones and derivatives can be obtained by above methods, many still have inherent drawbacks difficult to overcome. For example, some require tedious multi-step procedures,[2,3] some require rather harsh reaction conditions,[2,3,19,20] some require transition metal catalysts/ligands[4-9,11,13,16] that can lead to metal residue contaminant in the products and limit their applications in drug synthesis, and some require excess amounts of bases,[10,13] oxidants,[5,8,17] or reactants[19,20] that can lead to production of large amounts of wastes. Therefore, developing direct, efficient, atom-economic, and transition metal- and waste-free methods that can employ greener substrates and O_2 or even air as the oxidant are still of great importance in the field.



Scheme 1. General methods for quinazolinone skeleton construction.

On the other hand, it is well known amides can be readily obtained by nitrile hydration reaction,[21,22] which, also due to the

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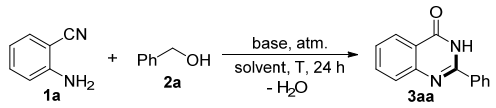
higher stability of nitriles than the corresponding amides, is known kinetically slower than amide hydrolysis to acids.[21] In this sense, the widely available *o*-aminoarylnitriles[23] may be a class of more preferable substrates, as the reaction efficiency may be enhanced by avoiding hydrolytic side-reactions of substrate *o*-aminoarylamides through *in situ* generation of intermediate *o*-aminoarylamides by nitrile hydration. With a long term interest in heterocycle construction[24] and developing alcohol-based green synthetic methods,[25] we have previously observed that base can catalyze the aerobic oxidation of alcohols[24f-g,25g] and that "cesium effect"[26] can lead to efficient and controllable CsOH-catalyzed nitrile hydration and aminolysis reactions.[22] We thus envisioned a new strategy for quinazolinone construction, i.e., a base-catalyzed aerobic oxidative annulation reaction of *o*-aminoarylnitriles with alcohols (Scheme 1G). Beside the advantages of using alcohols and *o*-aminoarylnitriles as the substrates, this reaction may also features high atom-economy, no transition metal contaminants in the products, and waste-free if O_2 or even air can be successfully used as effective oxidant as water would be the only by-product. To our knowledge, such a promising method has not been reported yet. Herein we report the detail of our findings.

Table 1. Condition screening and optimization.[a]



entry	base (mol%)	atm. (oxid.)	solv. (mL), temp.	**3aa**%[b]
1	CsOH (100)	air balloon	xylenes (3), 40~60 °C	36~73
2	***CsOH (100)***	***air balloon***	***xylenes (3), 80 °C***	***82***
3	CsOH (100)	air balloon	xylenes (3), 100~120 °C	72~75
4	CsOH (100)	air[c]	xylenes (3), 80 °C	67
5	CsOH (100)	O_2 balloon	xylenes (3), 80 °C	78
6	CsOH (100)	N_2	xylenes (3), 80 °C	0
7	-	air balloon	xylenes (3), 80 °C	0
8	base (100)[d]	air balloon	xylenes (3), 80 °C	0~69
9	CsOH (50)	air balloon	xylenes (3), 80 °C	46
10	CsOH (150)	air balloon	xylenes (3), 80 °C	71
11	CsOH (100)	air balloon	xylenes (1.5), 80 °C	64
12	CsOH (100)	air balloon	solvents (3),[e] 80 °C	0~79

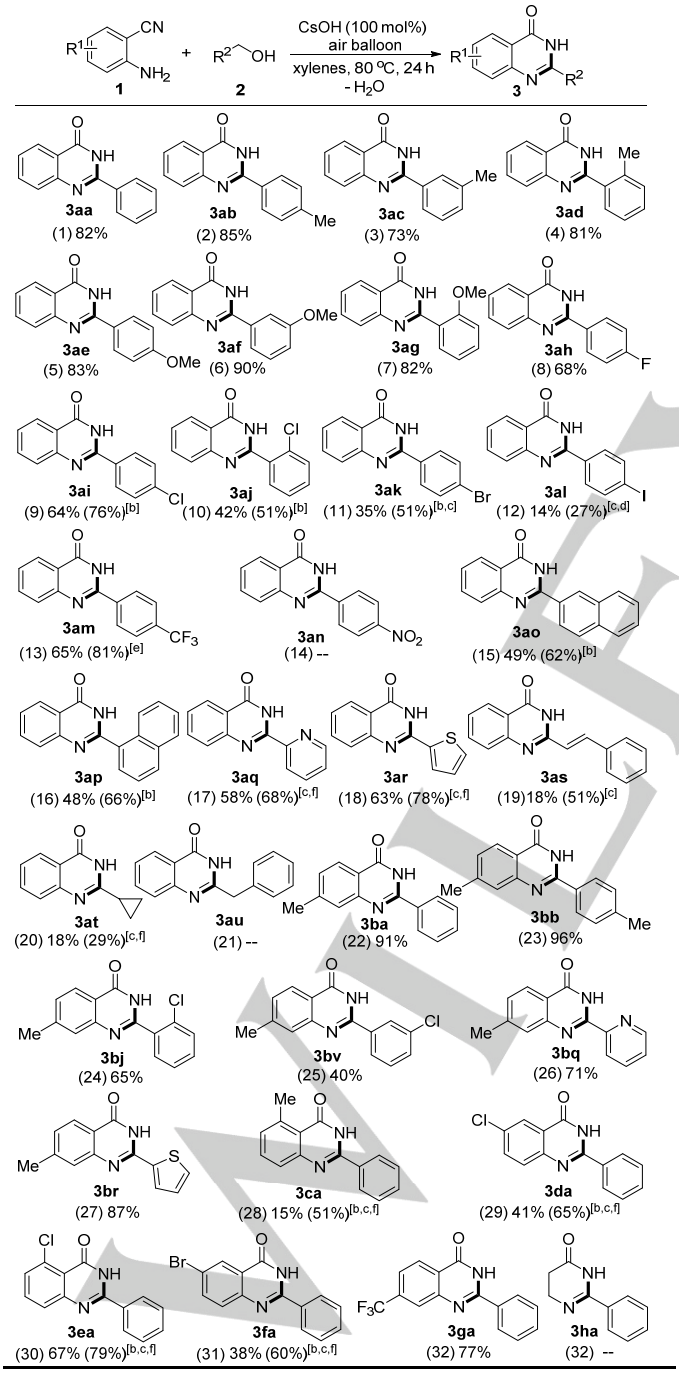
[a] The mixture of **1a** (1 mmol), **2a** (1.2 mmol), and a base ($CsOH·H_2O$ abbreviated as CsOH) in a solvent was sealed in a 100 mL Schlenk tube equipped with an air or O_2 balloon, heated for 24 h, and monitored by TLC/GC-MS. [b] Isolated yields based on **1a**. [c] Directly sealed without balloon. [d] NaOH: 59%; KOH: 64%; *t*-BuONa: 54%; *t*-BuOK: 69%; Cs_2CO_3: 0%. [e] Toluene: 78%; CH_3CN:58%; EtOH: 0%; DCM: trace; DMSO: 66%; dioxane: 79%.

We started the research by investigating the model reaction of *o*-aminobenzonitrile (**1a**) and benzyl alcohol (**2a**) (Table 1). The reaction was initially heated in xylenes at different temperatures using CsOH (1 equiv.) as the base and air (using an air balloon) as the oxidant (entries 1-3). The results showed that, with the increase of the reaction temperature, the yield of product **3aa** could be improved accordingly (entries 1-2), with 80 °C giving the highest yield of **3aa** (entry 2, 82%). At even higher temperatures, the product yield began to drop (entry 3), which may be due to over hydrolysis[21,22] of the nitrile substrate at higher temperatures. Then, the reaction was directly sealed under air without using the balloon (entry 4). Without adequate air, the reaction gave a lower yield of **3aa**, showing that the air amount is key to the reaction. Pure oxygen was also tested, but gave a slightly lower yield of 78% (entry 5). This indicates that air is even more effective than the more oxidative O_2. Therefore, the reaction can be safer, more economic, and more operable by employing air as the oxidant. Contrary to above conditions, the reaction under nitrogen gave no product at all (entry 6), suggesting this is indeed an aerobic reaction. Without CsOH, no reaction occurred either (entry 7), showing that base is crucial to the reaction. Then, various bases (NaOH, KOH, etc.) were screened to obtain the best one (entry 8), but gave only inferior product yields than CsOH, suggesting that CsOH is still the best base. The loading of CsOH was then investigated hoping to obtain a catalytic method. However, the reaction using less CsOH was much less effective (entry 9); while the reaction with more CsOH also gave a lower yield of **3aa** (entry 10), possibly due to nitrile over hydrolysis caused by excess amounts of the base.[21,22] The reaction was also investigated with higher concentration of the reactants using less solvent to enhance the reaction rate, but the results was not satisfactory (entry 11). Finally, a variety of solvents was also screened (entry 12). In comparison, xylenes were still the best solvent (entry 2).

The optimized conditions were then applied to various substrates to extend the scope of the method. As shown in Table 2, like the model reaction (entry 1), electron-rich benzylic alcohols including the sterically more bulky *ortho*-substituted ones (entries 4 and 7) generally gave good to high yields of the products (entries 2-7). The reactions of electron-deficient benzylic alcohols seemed to be less efficient. Thus, benzylic alcohols with more inert *para*-substituted fluoro, chloro, and trifluoromethyl groups could still give satisfactory yields of the products (entries 8-9, 13); whereas, those bearing sterically more bulky *ortho*-substituted ones and those with more reactive bromo and iodo groups gave lower yields of the products (entries 10-12). Modified conditions such as prolonged reaction time, elevated temperature, and increased loading of the substrates could improve the product yields obviously (entries 9-13). In contrast, *para*-nitrobenzyl alcohol did not gave any target product under a variety of conditions (entry 14), which may be due to the reactive nature of the nitro group under the basic conditions.[27] The reactions of the bulky naphthylmethanols were more sluggish, but afforded higher yields of the products in prolonged reaction time (entries 15-16). Similarly, heteroarylmethanols such as 2-pyridylmethanol and 2-thienylmethanol also afforded moderate yields of the products under the standard conditions and afforded higher yields of the

products under modified conditions (entries 17-18) as dioxane was also found as a good solvent for the reaction (Table 1, entry 12). In the case of allyl alcohols such as cinnamyl alcohol, its reaction required a higher temperature to achieve a satisfactory yield (entry 19). Aliphatic alcohols were then investigated. However, except the more reactive cyclopropylmethanol that afforded the product (entry 20), other aliphatic alcohols were found not reactive (entry 21), possibly due to their inactive nature toward the aerobic oxidation under the present conditions.

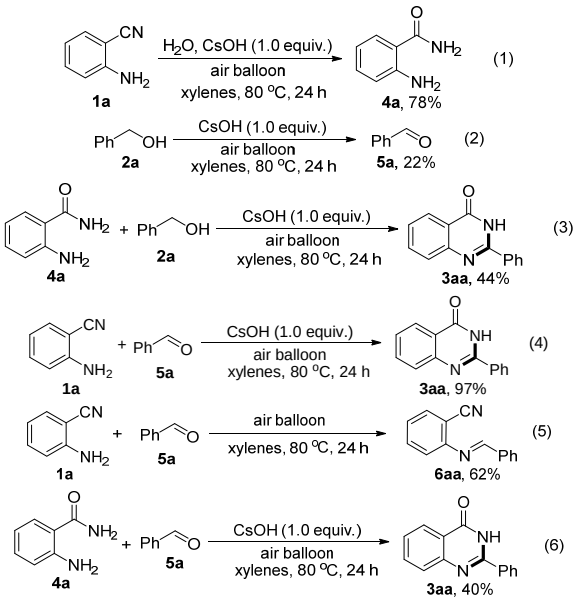
Table 2. Substrate Extension for CsOH-mediated aerobic oxidative annulation of *o*-aminoarylnitriles and alcohols.[a]



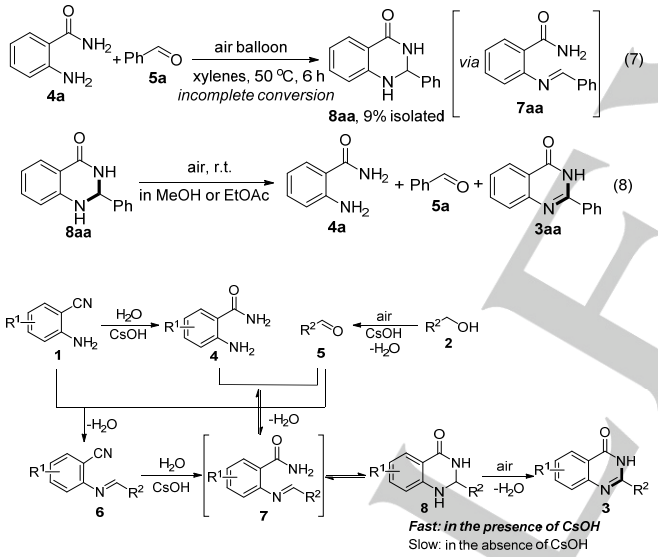
[a] See entry 2 of Table 1 for detail. Isolated yields based on **1**. [b] 36 h. [c] 120 °C. [d] 48 h. [e] 2 equiv. **1** added. [f] Dioxane used as the solvent.

The above method was then extended to substituted *o*-aminobenzonitriles. Even more efficient than unsubstituted **1a** (Table 2, entry 1), the electron-rich *p*-methyl-*o*-aminobenzonitrile **1b** afforded high yields of the products in reactions with unsubstituted alcohol **2a**, both electron-rich and –deficient benzylic alcohols, as well as the heteroarylmethanols (entries 22-26). In great contrast, the reaction of the sterically more bulky *o*-methyl-*o*-aminobenzonitrile **1c** was much ineffective, affording only the product in a moderate yield at a higher temperature using dioxane as the solvent (entry 27). This may be attributed to the hindered nitrile hydration step by the adjacent Me group in the reaction mechanism (vide infra). On the other hand, electron-deficient *o*-aminobenzonitriles could also afford the target products in satisfactory yields under the standard or modified conditions (entries 28-31). In addition to above *o*-aminoarylnitriles, an aliphatic nitrile (2-aminopropane nitrile) was also tested, but no product was obtained under the present conditions (entry 32).

Control reactions were then investigated to probe the reaction mechanism and the role of CsOH in the reaction.[28] Firstly, *o*-aminobenzonitrile **1a** and benzyl alcohol **2a** effectively afforded *o*-aminobenzamide **4a** and benzaldehyde **5a** respectively by hydration and aerobic oxidation reactions in the presence of CsOH (eqs. 1-2). The reaction of **4a** and **2a** also afforded **3aa** under the standard conditions (eq. 3). In contrast, all the above reactions did not occur without CsOH, suggesting the key role of CsOH in the nitrile hydration[22] and aerobic alcohol oxidation[24f-g,25g,29] steps. Then, the reaction of **1a** and **5a** under the standard conditions effectively afforded **3aa** in a high yield of 97% (eq. 4); whereas, in the absence of CsOH, the reaction afforded only the condensed imine **6aa** in a moderate yield (eq. 5). This suggests that condensation of **1** and **5** can readily take place to give imine intermediates **6**, but CsOH is key to facilitate its annulation to product **3**.



The reaction of **4a** and **5a** was then investigated in the presence of CsOH, which afforded **3aa** in 40% yield (eq. 6). Herein the yields of **3aa** obtained from the reactions of *o*-aminobenzamide **4a** (eqs. 3 and 6) are clearly much lower than those from *o*-aminobenzonitrile **1a** (the standard reaction in Table 1 and eq. 4), which may be due to the amide hydrolysis to acid in the presence of a base, a difficult-to-avoid side reaction of nitrile hydration.[21] This further suggests that *o*-aminobenzonitriles **1** are more advantageous substrates than *o*-aminobenzamides **4** in the present reaction. In contrast, without CsOH, instead of producing **3aa**, a considerable amount of a new product was observed in an incomplete reaction of **4a** and **5a**, which, possibly *via* formation imine intermediate **7aa**, was determined to be annulated **8aa** as confirmed by GC-MS and NMR analysis (eq. 7).[4,28] As we have also observed, the low yield of **8aa** in this reaction may be attributed to the incomplete reaction of **4a** and **5a**, **8aa**'s easy decomposition to reactants **4a** and **5a** and slow oxidation to **3aa** in the presence of air (eq. 8).[28] Therefore, it may be concluded from above contrastive reactions (eqs. 6-8) that, without CsOH, the blank reaction of **4** and **5** giving **8** is an equilibrium[4] and further aerobic oxidation of **8** to **3** is a slow process. In contrast, the annulation of **4** and **5** can be greatly facilitated by CsOH to finally afford product **3** via a CsOH-promoted aerobic oxidation of intermediate **8**.



Scheme 2. Plausible reaction paths for the CsOH-mediated aerobic oxidative cascade annulation of alcohols with *o*-aminoarylnitriles.

Based on above results, possible reaction paths for the CsOH-mediated aerobic oxidative cascade annulation of alcohols and *o*-aminoarylnitriles were proposed. As shown in Scheme 2, *o*-aminoarylnitriles **1** and alcohols **2** may firstly be transformed into the corresponding *o*-aminobenzamides **4** and aldehydes **5** respectively via CsOH-mediated nitrile hydration and aerobic alcohol oxidation reactions. Then, the remained unhydrated *o*-aminoarylnitriles **1** or *o*-aminobenzamides **4** may react with aldehydes **5** to give condensed imine intermediates **6** or **7**, which may quickly undergo oxidative annulation to afford product quinazolinones **3** via the formation of another intermeiate **8**. Although the blank reaction of **4** and **5** may be an equilibrium and **8** tends to decompose back to **4** and **5**, in the presence of CsOH, fast aerobic oxidation of **8** to **3** can drive the reaction go forward and finally afford the quinazolinones **3**.

In conclusion, we developed a mild and atom-economic method for direct and efficient synthesis of quinazolinones via a transition metal-free aerobic oxidative cascade annulation reaction of the widely available and stable *o*-aminoarylnitriles and alcohols. In this reaction, air can be employed as an effective oxidant under a mild condition, generating water as the only byproduct. Meanwhile, possibly owing to the "cesium effect", the water soluble CsOH is the best base as it's found crucial in all the key steps of the reaction mechanism. Since a wide range of substrates can be used to prepare substituted quinazolinones without contamination by transition metal residues, this method may be of potential applications in pharmaceutical synthesis. Further extensions of this transition metal-free base-catalyzed construction of heterocycles using readily available and economic starting materials are underway in this laboratory.

Experimental Section

Typical Procedure for CsOH-Mediated Aerobic Oxidative Casecade Annulation of Alcohols with *o*-Aminoarylnitriles. The mixture of *o*-aminobenzontrile (**1a**) (0.1181 g, 1.0 mmol), benzyl alcohol (**2a**) (0.1296 g, 1.2 mmol, 1.2 equiv.), and CsOH·H_2O (0.1679 g, 1.0 equiv.) in xylenes (3.0 mL) in a Schlenk tube (100 mL) equipped with an air balloon was heated at 80 °C for 24 h and monitored by TLC and/or GC-MS. The mixture was then quenched by aqueous HCl (1 M, 2 mL) and extracted with ethyl acetate. The solvent was evaporated under vacuum. The residue was then purified by flash column chromatography on silica gel using petroleum ether and ethyl acetate (5:1) as the eluent, giving the target **3aa** in 82% isolated yield.

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Keywords: aerobic oxidation • air • alcohols • *o*-aminobenzonitriles • cascade annulation • quinazolinones

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Entry for the Table of Contents

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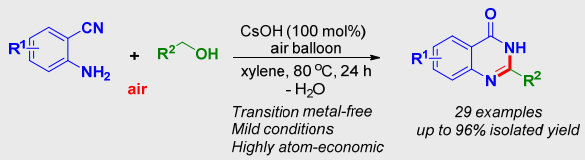

A mild and atom-economic method is developed for direct and efficient synthesis of quinazolinones via a transition metal-free aerobic oxidative cascade annulation reaction of the widely available *o*-aminoarylnitriles and alcohols. Air can be employed as an effective oxidant under mild conditions, generating water as the only byproduct. Possibly owing to the "cesium effect", the water soluble CsOH is the best base as it's found crucial in all the key steps of the reaction mechanism. Since a wide range of substrates can be used to prepare substituted quinazolinones without contamination by transition metal residues, this method may be of potential applications in pharmaceutical synthesis. Possible reaction paths were also proposed according to the control reactions.

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