FULL PAPER DOI: 10.1002/adsc.202001535

Advanced Synthesis & Catalysis

Copper-Catalyzed Three-Component Cascade Reaction of Benzaldehyde with Benzylamine and Hydroxylamine or Aniline: Synthesis of 1,2,4-Oxadiazoles and Quinazolines

Chao Wang,[+a] Xiyan Rui,[+a] Dongjuan Si,[a] Rupeng Dai,[a] Yueyue Zhu,[a] Hongmei Wen,[a] Wei Li,[a,*] and Jian Liu[a,*]

[a] School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, People's Republic of China
E-mail: liujian623@njucm.edu.cn; liwaii@126.com

[+] Chao Wang and Xiyan Rui contributed equally.

Manuscript received: December 9, 2020; Revised manuscript received: March 2, 2021;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202001535

Abstract: The analogous three-component synthesis strategy for substituted 1,2,4-oxadiazole and quinazoline derivatives from readily available benzaldehyde, benzylamine and hydroxylamine or aniline has been developed. Both the cascade reaction sequences involves nucleophilic addition of C–N bond, introduction a halogen donor, nucleophilic substitution and Cu(II)-catalyzed aerobic oxidation. This synthesis methodology demonstrated good yields, broad substrate scope and oxygen as a green oxidant. Thus, this synthesis protocol provides strategies for the construction of substituted 1,2,4-oxadiazole and quinazolines from readily and simple starting materials.

Keywords: 1,2,4-oxadiazole; quinazoline; three-component; aerobic oxidation

Introduction

The nitrogen heterocycles and oxygen heterocycles are privileged scaffolds existed in numerous natural products and synthetic molecules which produce bioactivity and pharmacological activity. Because of the wide coverage of activities and unique properties, two pharmacophores, named 1,2,4-oxadiazoles and quinazolines, have been attracting much attention.[1] The substituted 1,2,4-oxadiazole derivatives exhibited anti-inflammatory, anti-depressant and anti-cancer activities, etc (Figure 1 a).[2] For example, **Oxolamine** was described and introduced as a cough suppressant, recently **Ataluren** (**PTC124**) has been launched for the therapy of Duchenne muscular dystrophy.[3] Besides, quinazoline-based compounds also possess a broad spectrum of pharmacological activities, including anti-inflammatory, anti-microbial, anti-malarial, anti-convulsant, antiviral and anti-cancer activities, etc (Figure 1 b).[4] As well-known anticancer drugs **Gefitinib** and **Erlotinib**, which contained unique quinazoline scaffolds, have been approved for the treatment of non-small cell lung cancer (NSCLC).[5]

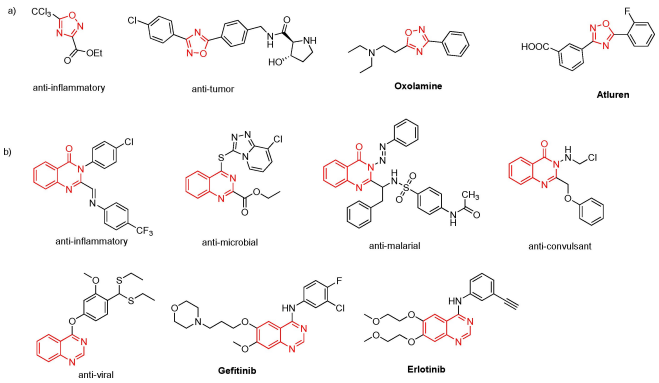


Figure 1. Example of useful 1,2,4-oxadiazole (a) and quinazoline (b) molecules.

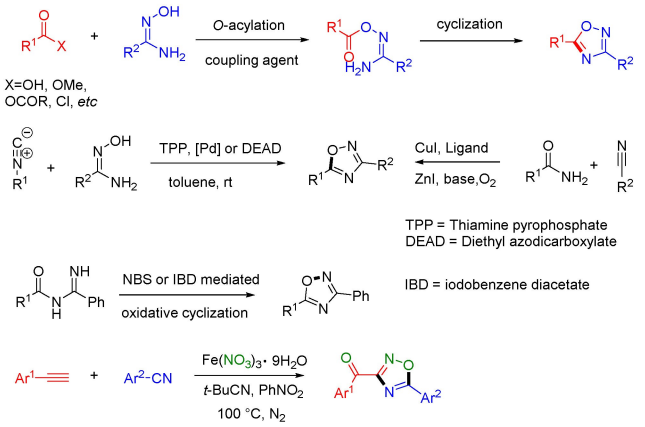
Previous studies reported several methods to synthesize 1,2,4-oxadiazole and quinazoline derivatives. As for the 1,2,4-oxadiazole, the traditional synthesis protocol contains two steps: 1) *O*-acylation of an amidoxime, which can be easily prepared by the reaction of activated carboxylic acid derivatives such

as acid chlorides, esters and anhydrides; 2) intramolecular dehydration of the *O*-acyl amidoxime with bases (Scheme 1 a).[6] Recently, the 5-amino-1,2,4-oxadiazole products are obtained by the insertion of cyano or isocyanide.[7] Additionally, some works focused on transforming substrates that contained amidine/guanidinium group to 1,2,4-oxadiazole scaffold by NBS/iodobenzene diacetate (IBD)-mediated oxidative cyclization.[8] The latest synthesis strategy uses iron (III) nitrate to mediate the 1,3-dipolarization of alkynes and nitriles, the iron (III) nitrate plays dual roles in the nitration of alkynes and the activation of nitriles.[9]

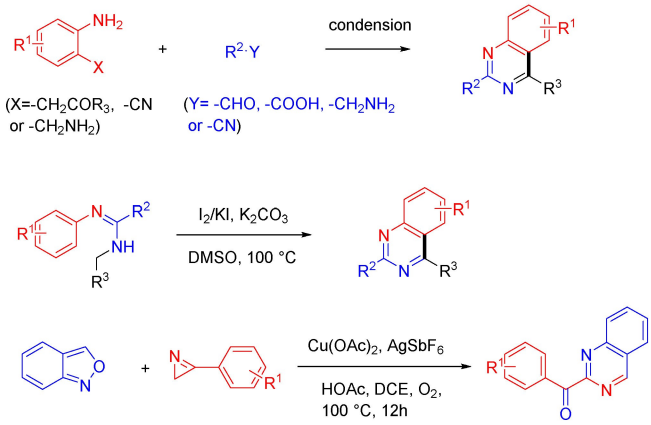
Meanwhile, the general synthesis procedure for quinazoline is the condensing of different *ortho*-functionalized anilines (2-carbonylaniline,[10a,b,c,d] 2-aminobenzylamine[10e,f] or 2-aminobenzonitrile[10g,h]) with benzaldehyde, benzylamine, benzoic acid or benzonitrile (Scheme 1 b). Moreover, another feasible method is the oxidative cyclization of arylamidines with I_2-mediated C–C bond, and the later one was formatted from C(sp^3)–H and C(sp^2)–H bonds.[11] Other reagents such as 2-ethynylanilines, 2-alkylaminobenzonitriles, aryl diazonium salts, *N*-sulfinylimines, imines and amidines are identified as alternative substrates in the synthesis of various substituted quinazoline derivatives.[12] Recently, Xie reported a Cu/Ag-catalyzed annulation of 3-aryl-2*H*-azirines with anthranils to provide (quinazolin-2-yl)methanone derivatives.[13] Although the strategy showed significant advancements in terms of 1,2,4-oxadiazole and quinazoline syntheses, most of these procedures had drawbacks such as time-consuming, harsh reaction conditions, special starting materials, multi-step procedures, and expensive transition metal complexes, ligands, additives, oxidants, which significantly hindered their further application. Most importantly, there is rarely a general synthesis strategy has been reported for these two heterocyclic scaffolds under the similar reaction conditions.

Multicomponent cascade reaction serves as one of the most important synthetic strategies for the green access to nitrogen heterocycles, which eliminates the purification steps of intermediates and decreases the discrete chemical steps, waste products and operation costs.[14] Recently, the large amounts of oxidants such as organohalide, $PhI(OAc)_2$, benzoquinone and metal salts (Ag or Cu) are utilized to construct nitrogen-containing heterocycles through transition-metal-catalyzed C–N bond formation and annulation.[15,16,17] There is no doubt that these methods will suffer from numerous limitations in organic synthesis due to their high price, toxicity and unfriendly environmental propoerties.[17,18] Molecular oxygen is an atom-economical, abundant, and environmental-friendly energy,[19] nowadays some researchers report using copper-catalyzed aerobic oxidation to construct oxygen, nitrogen, and sulfur-incorporated heterocycles.[20] Meanwhile, in 2016 Arndtsen described that the selective aerobic oxidation of amines to nitriles and imines through CuI- or $CuPF_6$-catalyzed in different solvents.[21] As our investigation so far, the synthesis of 1,2,4-oxadiazole and quinazoline from easily starting material benzylamine, benzaldehyde, hydroxylamine or aniline, has not yet been explored by using similar synthesis strategy. Herein, we report a new strategy of analogous three-component cascade reaction to yield 1,2,4-oxadiazole and quinazoline scaffold, which possess [2+2+1] annulation and [3+2+1] annulation *via* a Cu(II)-catalyzed dehydrogenative cyclization (Scheme 1 c). This three-component cascade annulation can

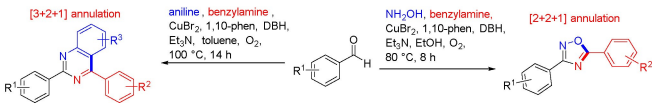
a). Preparation of 1,2,4-oxadiazoles



b). Preparation of quinazolines



c). This work:



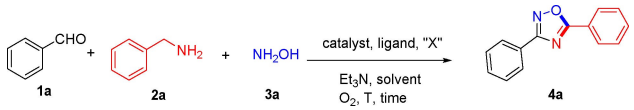
Scheme 1. Synthetic strategies for 1,2,4-oxadiazole and quinazoline.

be developed as an access to 1,2,4-oxadiazoles and quinazolines.

Result and Discussion

The benzaldehyde (**1a**), benzylamine (**2a**) and hydroxylamine (**3a**) are easy-access materials and all of them are widely utilized as key synthons in nitrogen-containing functional molecular synthesis. We initiate our studies by evaluating the feasibility of the three-component cascade reaction of the benzaldehyde (**1a**), benzylamine (**2a**) and hydroxylamine (**3a**) for the 1,2,4-oxadiazole synthesis in the presence of $CuBr_2$-mediated aerobic oxidation (Table 1). The three-component [2+2+1] cascade annulation of 1,2,4-oxadiazole involves: nucleophilic addition of C–N bond, introduction of a halogen donor, nucleophilic substitution and Cu(II)-catalyzed aerobic oxidation. Therefore, the solvent plays a critical role in the three-component cascade transformation. The desired product **4a** can be obtained in 10% yield (entry 1) when toluene was used as the solvent. While other solvents such as DMSO, THF, MeOH, isopropanol and HFIP, didn't change the reaction activities essentially (entries 2–8). Surprisingly, the isolated yield of target product **6a** boosted up to 35% and 40%, respectively, once H_2O and EtOH was used as the solvent, and the EtOH is selected as the best solvent for the synthesis protocol of 1,2,4-oxadiazole. Meanwhile, the halogen donor "X" is also incorporated in the reaction process. By investigating the various halogen donor, the dibromohydantoin (DBH) is selected as the optimal halogen donor, and the yield of **4a** was up to 65% (entries 9–11). The key step for cascade reaction is the Cu (II)-mediated oxygen dehydrogenative coupling. Different copper salt including CuI, $Cu(OAc)_2$ and different ligands, for instance, pyridine, bipyridine and 1,10-phenanthroline (1,10-phen) are conducted to further improve the yield of the target product **4a** (entries 12–15). As we expected, the yield of **4a** is enhanced to 90% by using 1,10-phen as a ligand, whereas other catalysts (CuI, $Cu(OAc)_2$) are ineffective. Besides, the reaction proceed difficu without oxygen, which indicates the oxygen as an essential role in this reaction (entries 16, 17). We also explored the reaction time and reaction temperature, and the optimal reaction time was 8 hours and the reaction temperature was 80 °C (See the Supporting Information for details).

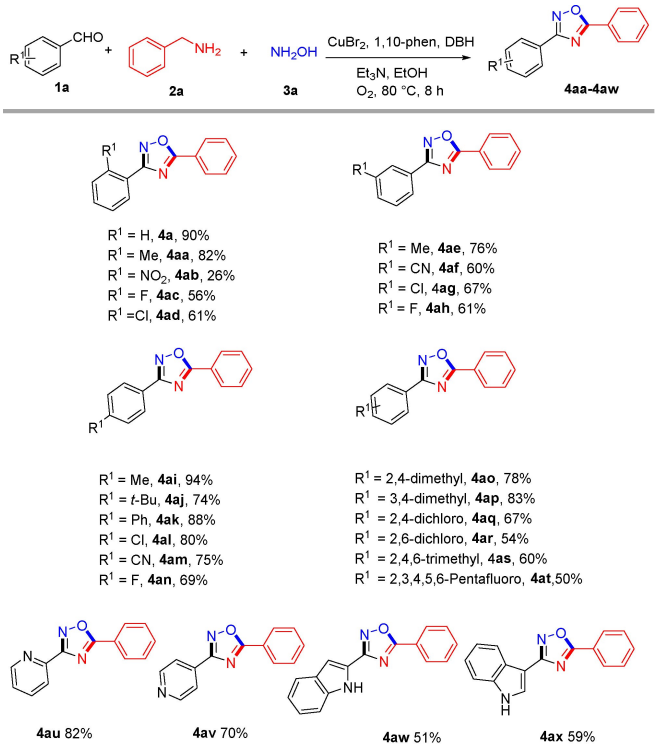
Table 1. Optimization of the synthesis of 1,2,4-oxadiazole **4a**.[a]



Entry	Catalyst	Ligand	"X"	Solvent	Yield (%)[b]
1	$CuBr_2$	pyridine	NCS[c]	toluene	10
2	$CuBr_2$	pyridine	NCS	DMSO	Trace
3	$CuBr_2$	pyridine	NCS	THF	15
4	$CuBr_2$	pyridine	NCS	EtOH	40
5	$CuBr_2$	pyridine	NCS	MeOH	23
6	$CuBr_2$	pyridine	NCS	H_2O	35
7	$CuBr_2$	pyridine	NCS	isopropanol	17
8	$CuBr_2$	pyridine	NCS	HFIP	Trace
9	$CuBr_2$	pyridine	NBS[d]	EtOH	45
10	$CuBr_2$	pyridine	I_2	EtOH	32
11	$CuBr_2$	pyridine	DBH[e]	EtOH	65
12	CuI	pyridine	DBH	EtOH	13
13	$Cu(OAc)_2$	pyridine	DBH	EtOH	Trace
14	$CuBr_2$	bipyridine	DBH	EtOH	75
15	$CuBr_2$	1,10-phen	DBH	EtOH	90
16[f]	$CuBr_2$	1,10-phen	DBH	EtOH	22
17[g]	$CuBr_2$	1,10-phen	DBH	EtOH	0

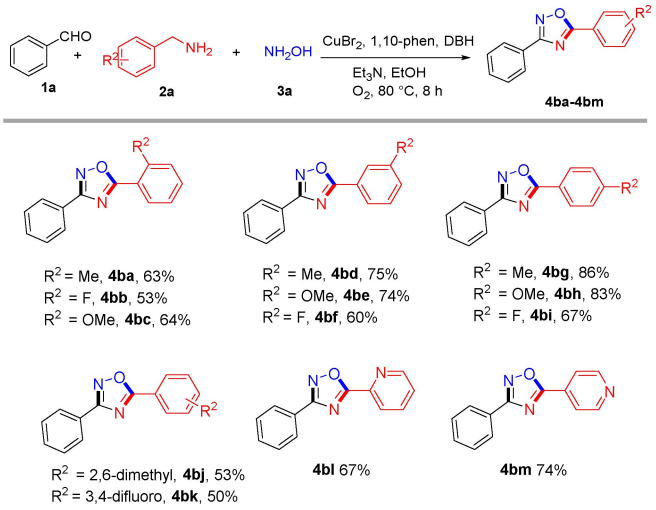
[a] Reaction conditions: benzaldehyde (**1a**, 0.5 mmol), benzylamine (**2a**, 0.5 mmol), hydroxylamine (**3a**, 0.5 mmol), catalyst (10 mmol%), ligand (20 mmol%), Et_3N (0.5 mmol), "X" (0.5 mmol) and solvent (4.0 mL) were stirred at 80 °C under O_2 for 8 h;
[b] Isolated yield;
[c] NCS = *N*-Chlorosuccinimide;
[d] NBS = *N*-bromosuccinimide;
[e] DBH = dibromohydantoin;
[f] The reaction was carried out under air atmosphere.
[g] The reaction was carried out under N_2 atmosphere.

After we optimized the reaction conditions, the scope and generality of this three-component [2+2+1] cascade annulation was initiated observing various substituted benzaldehyde derivatives (Scheme 2). Interestingly, the target product **4aa** bearing *o*-methyl could be obtained in a high yield (82%), and the halogen functional groups involving fluorine and chlorine were well tolerated to afford the corresponding annulated products in moderate yields (**4ac**: 56%; **4ad**: 61%). However, the *o*-NO_2 precursor generated the desired product **4ab** in only poor yield of 26%. In summary, as for the *ortho*-substituent, the reaction efficiency was inhibited by the strong electron-withdrawing substituent, on the contrary the reaction activity was enhanced by the electron-rich groups. A similar trend was also revealed for the *meta*-substituted substrates reaction efficiencies, the electron-rich groups (**4ae**: 76%) performed relatively better than the electron-deficient groups (**4af**: 60%; **4ag**: 67%; **4ah**: 61%). Besides, the small electron-donating substituent was beneficial to the transformation of 1,2,4-oxadiazole, as a result the yield of product **4ai** bearing *p*-methyl was promoted to 94%. Whereas the substrate containing a *tert*-butyl substituent decreased in their reaction efficiencies because of the steric hindrance phenomena (**4aj**: 75%). Interestingly, other electron-deficient groups involving phenyl, chlorine, fluorine and cyano group were also tolerated for this transformation, the yield of **4a** was slightly decreased



[a] Reaction conditions: benzaldehyde (**1**, 0.5 mmol), benzylamine (**2a**, 0.5 mmol), hydroxylamine (**3a**, 0.5 mmol), $CuBr_2$ (10 mmol%), 1,10-phen (20 mmol%), DBH (0.5 mmol), Et_3N (0.5 mmol) and EtOH (4.0 mL) were stirred at 80 °C under O_2 for 8 h; [b] Isolated yield.

Scheme 2. Substrate Scope of benzaldehyde.[a,b]



[a] Reaction conditions: benzaldehyde (**1a**, 0.5 mmol), benzylamine (**2**, 0.5 mmol), hydroxylamine (**3a**, 0.5 mmol), $CuBr_2$ (10 mmol%), 1,10-phen (20 mmol%), DBH (0.5 mmol), Et_3N (0.5 mmol) and EtOH (4.0 mL) were stirred at 80 °C under O_2 for 8 h; [b] Isolated yield.

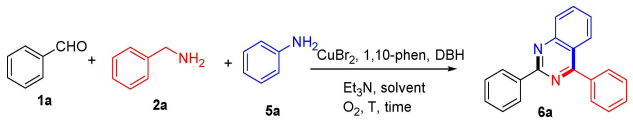
Scheme 3. Substrate Scope of benzylamine.[a,b]

(**4ak**: 88%; **4al**: 80%; **4an**: 69%; **4am**: 75% *vs* **4a**: 90%). Furthermore, the corresponding yield of *di*-substituted, *tri*-substituted and *pent*-substituted substrates that were combined with various substituents were decreased (**4ao**: 78%; **4ap**: 83%; **4aq**: 67%; **4ar**: 54%; **4as**: 60%; **4at**: 50%), indicating that the steric hindrance phenomena of plays a critical role to influence the yield of 1,2,4-oxadiazole. Other aryl-functionalized benzaldehydes were also undergoing the transformation easily, the yields of the corresponding products were ranging from 51% to 82% (**4au**–**4ax**). In summary, the benzaldehyde substrates bearing small electron-rich groups were favourable for the 1,2,4-oxadiazole preparation, but the bulkier substituents were not suitable, thus the electron effect and steric hindrance both influenced the reaction efficiency.

Benzylamine **2a** also contributed greatly to this reaction, and the effects of different benzylamine derivatives bearing various substituents were explored (Scheme 3). In general, *mono*-substituted benzylamine derivatives, show better yield of target product with electron-donating groups such as methyl and methoxy than those with electron-withdrawing substituents such as fluorine (**4ba**, **4bc** *vs* **4bb**; **4bd**, **4be** *vs* **4bf**; **4bg**, **4bh** *vs* **4bi**). Among these compounds, the substrates bearing *p*-Me and *p*-OMe exhibited the best reaction activity (**4bg**: 86%; **4bh**: 83%). Interestingly, the steric effect was also investigated while the substituents were located at the *ortho*-position, especially the target product **4aj** was furnished in only 53% yield while the 2,6-dimethyl benzylamine was employed. Notably, compared to the 3-F-benzylamine (**4bf**) and 4-F-benzylamine substrate (**4bi**), the reaction efficiency was decreased while the substrate containing a 3,4-difluoro unit (**4bk**: 50%), and this may due to the fact that the two fluorine atoms strongly reduced the electronic density of benzene ring. Similarly, other aryl-functionalized benzylamines involving pyridine ring were also incorporated into this transformation, the yield of desired product **4bl** and **4bm** were 67% and 74%, respectively. In conclusion, substituted benzylamine derivatives exhibited the similar trend to the benzaldehyde substrates, that the small electron-donating group enhanced the reaction ability while the bulkier substituent was not tolerated for this transformation.

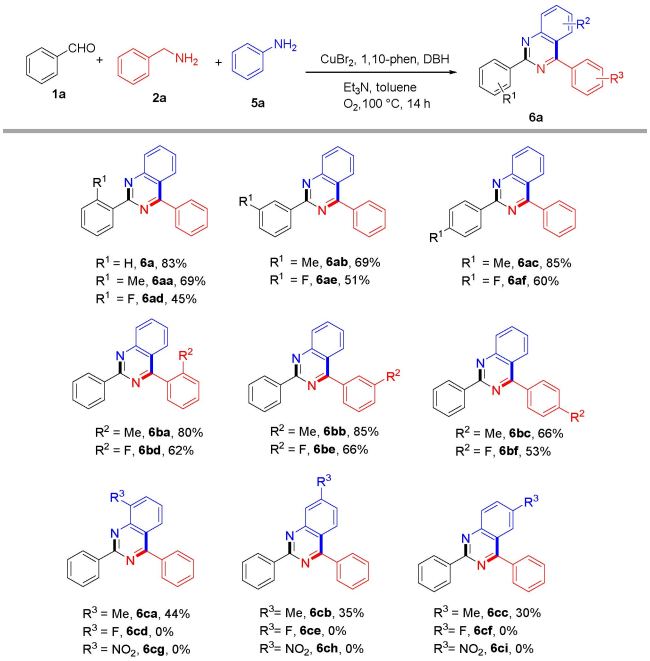
The aniline was also utilized as an essential material for the construction of the nitrogen-containing heterocycle, while the starting material hydroxylamine **3** was replaced by the aniline **5** for the first step of C=N formation, the one-step synthesis of 1,2,4-oxadiazole **4** was easily extended for the synthesis of quinazoline **6** (Table 2). We initiated our studies by repeating the optimized reaction conditions for the 1,2,4-oxadiazole synthesis, and the desired quinazoline **6** could be obtained in 22% yield (entry 1). It is potential that the solvent may significantly affect the reaction efficiency, so we screened various solvent and tried to enhanced reaction activity (entry 2–4). The

Table 2. Optimization of the synthesis of quinazoline **6a**.[a]



Entry	T (°C)	time (h)	Solvent	Yield (%)[b]
1	80	8	EtOH	22
2	80	8	H_2O	10
3	80	8	DMSO	35
4	80	8	Toluene	56
5	60	8	Toluene	37
6	90	8	Toluene	61
7	100	8	Toluene	67
8	110	8	Toluene	58
9	100	6	Toluene	47
10	100	10	Toluene	63
11	100	12	Toluene	76
12	100	14	Toluene	83
13	100	16	Toluene	82
14[c]	100	14	Toluene	0

[a] Reaction conditions: benzaldehyde (**1a**, 0.5 mmol), benzylamine (**2a**, 0.6 mmol), aniline (**5a**, 0.5 mmol), $CuBr_2$ (10 mmol%), 1,10-phen (20 mmol%), DBH (0.5 mmol), Et_3N (0.5 mmol) and solvent (4.0 mL) were stirred at T °C under O_2 for time;
[b] Isolated yield.
[c] The reaction was carried out under an air atmosphere or N_2 atmosphere.



[a] Reaction conditions: benzaldehyde (**1**, 0.5 mmol), benzylamine (**2a**, 0.5 mmol), aniline (**5**, 0.5 mmol), $CuBr_2$ (10 mmol%), 1,10-phen (20 mmol%), DBH (0.5 mmol), Et_3N (0.5 mmol) and toluene (4.0 mL) at 100°C under O_2 for 14 h; [b] Isolated yield.

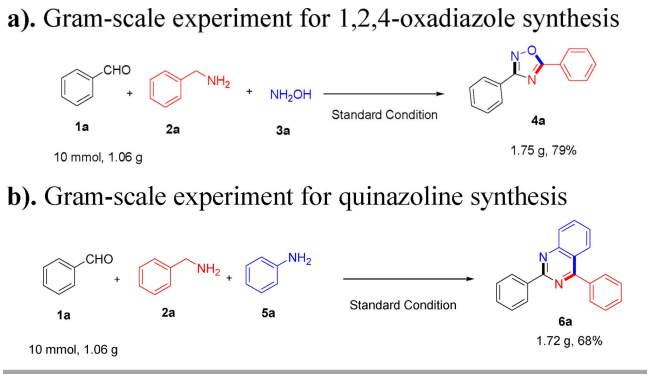
Scheme 4. Synthesis of quinazoline derivatives.[a,b]

yield of product **6a** could promote to 56% while the toluene was used as the solvent. Encouraged by this result, lower product yield was observed at lower reaction temperature. On the contrary, enhancing the temperature helped to improve the reaction efficiency, and the optimal reaction temperature was found to be 100 °C which resulted in the yield of product **6a** increasing to 67% (entry 5–8). Interestingly, through the exploring of the cascade reaction time, a relative higher yield could attain to 84% when the reaction time was extended to 14 h (entry 9–13). On the contrary, the reaction activity was inhibited while the reaction was carried out under an air or N_2 environment (entry 14). Through the inspecting of other reaction conditions (Supporting Information), the optimal reaction conditions could be identified as following: the catalyst was $CuBr_2$, the ligand was 1,10-phen, the halogen-donor was DBH, the solvent was toluene, the reaction temperature and time were 100 °C and 14 h respectively. Most importantly, the oxygen environment was critical to this three-component cascade reaction.

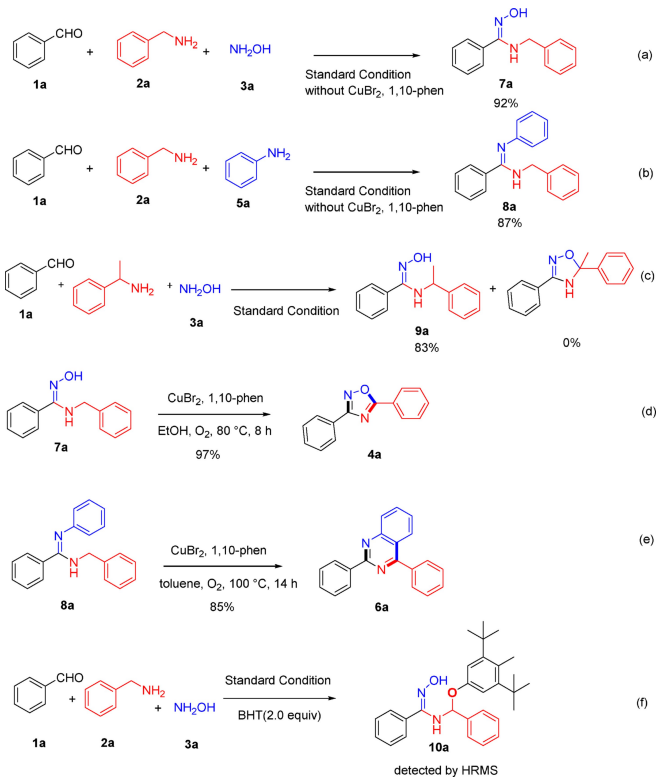
The optimized reaction conditions were employed for the synthesis of other quinazoline derivatives **6** by utilizing diverse libraries of benzaldehyde **1a**, benzylamine **2a** and aniline **5a** for this three-component [3 + 2 + 1] annulation (Scheme 4). Generally, as for different benzaldehyde analogues, the desired quinazoline products **6aa**–**6af** were obtained at yields ranging from 44% to 86%. The substrate with electron-rich substituents reacted smoother than the substrate with electron-deficient groups (**6aa**: 69% > **6ad**: 45%; **6ab**: 69% > **6ae**: 51%; **6ac**: 85% > **6af**: 60%). The substituents at *para*-position exhibited better reaction efficiency than those at *ortho*-position and *meta*-position. Besides, the benzylamine analogues with the same substituent at different positions also exhibited the similar trend that the substrate with electron-donating groups were more favourable for this transformation, and the substrate containing an electron-withdrawing substituent provided relatively lower yield for the desired product. Among these quinazoline derivatives **6ba**–**6bf**, the reaction ability of *meta*-substituted compounds was better than the corresponding *ortho*- or *para*-substituted compounds regardless of electron-withdrawing or electron-donating substituents. However, as for the aniline derivatives, the transformation could only be achieved by the compounds involving electron-donating substituents such as methyl (**6ca**: 44%; **6cb**: 35%; **6cc**: 30%), and it was very difficult for substrates containing electron-withdrawing groups involving fluorine or nitro to accomplish this transformation. In summary, the electron effect was critical to this [3 + 2 + 1] annulation, the electron-donating substituents were well tolerated in the present

reaction system, furnishing the corresponding products in good to moderate yields. However, while the substrate containing electron-withdrawing groups, the three-component cascade reaction proceeded difficulty to afford the quinazoline product.

To further verify the synthetic utility of this reaction, a gram-scale three-component [2+2+1] cascade annulation of 1,2,4-oxadiazole **4a** was carried out under the standard reaction conditions (Scheme 5). To our delight, the desired 1,2,4-oxadiazole **4a** was provided in 79% yield (1.75 g) while the reaction was performed on a 10 mmol scale. Similarly, this three-component [3+2+1] annulation of quinazoline **6a**



Scheme 5. Further Studies of the Reaction.

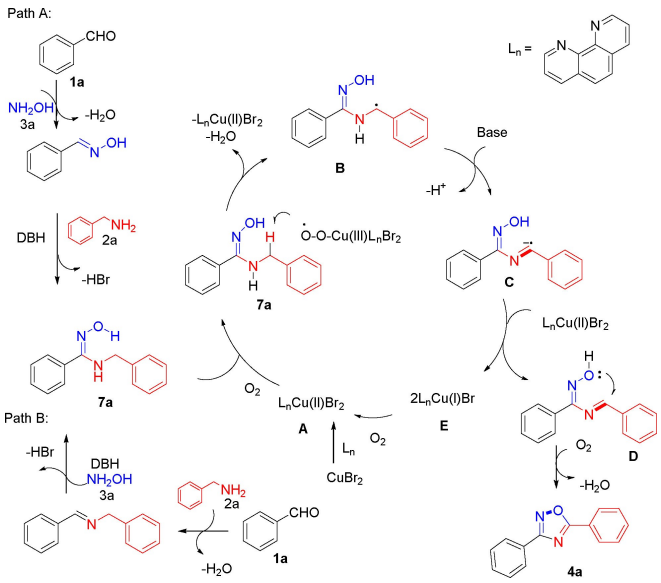


Scheme 6. Control Experiments.

was also proceeded smoothly on a gram-scale, we could provide the target quinazoline **6a** in 68% yield (1.72 g) on a 10 mmol scale. As a result, the yield for gram-scale was lower than obtained in the small-scale.

To provide insight into the mechanism of these reactions, several control experiments were designed and performed. In the synthesis process of 1,2,4-oxadiazole product **4a**, regardless of the reaction route, the benzylamine or hydroxylamine mainly nucleophilic attack the halogen donor to yield the intermediate **7a** which was identified as the precursor of 1,2,4-oxadiazole heterocycles **4a**. When the reaction was performed in the absence of $CuBr_2$ and 1,10-phen (Scheme 6a), the intermediate **7a** was furnished in 92% yield through the condensation and substitution of benzaldehyde **1a**, benzylamine **2a** and hydroxylamine **3a**. The product 1,2,4-oxadiazole was generated by eliminating two molecules of hydrogen *via* copper-mediated O_2 dehydrogenative coupling from the intermediate **7a**. Similarly, the cascade annulation to obtain quinazoline **6a** revealed the analogous reaction process, the yield of intermediate **8a** was 87% in the absence of $CuBr_2$ and 1,10-phen (Scheme 6b). However, the reaction ceased at the stage of nucleophilic substitution of methylbenzylamine owing to the failure of Cu(II)-catalyzed aerobic dehydrogenative cyclization when replacing the benzylamine by methylbenzylamine under standard reaction conditions (Scheme 6c), and the corresponding product **9a** was obtained in 83% yield. Furthermore, the isolated intermediate **7a** and **8a** were processed an elimination reaction through Cu(II)-catalyzed aerobic dehydrogenative annulation (Scheme 6d and 6e), the yield of the corresponding 1,2,4-oxadiazole product **4a** and quinazoline **6a** were 97% and 85%, respectively. In addition, butylated hydroxytoluene (BHT, 2.0 equiv.) as radical scavengers was added into the reaction system under the standard conditions. As a result, **10a** was determined by HRMS, indicating that the reaction proceeded *via* a radical pathway (Scheme 6f).

According to the results of these experiments, and refer to some related studies that have been reported,[22] a plausible mechanism was proposed for the present three-component [2+2+1] cascade annulation of 1,2,4-oxadiazole **4a** synthesis (Scheme 7). The critical precursor of cyclization **7a** was obtained through nucleophilic addition and nucleophilic substitution regardless **Path A** or **Path B**. Presumably, the 1,10-phen was identified as a ligand and coordinated with $CuBr_2$ to provide a five-membered copper metallacycle **A**. Subsequently, the aerobic oxidation was proceeded by depriving the hydrogen radicals from the **7a** to generate the radical intermediate **B**, which initially undergo a process of oxidating of Cu(II)-complex **A** through oxygen. Then proton was removed *via* base-mediated intramolecular elimination to afford the electron-rich C=N intermediate **C**. Through the Cu-



Scheme 7. Proposed Reaction Mechanism of 1,2,4-oxadiazole Synthesis.

promoted electron transfer, the intermediate **D** was obtained. Finally, the target 1,2,4-oxadiazole product was yielded through the intramolecular addition and elimination of intermediate **D**, the reoxidation of the Cu(I)-complex to the Cu(II)-complex would be utilized for the next catalytic cycle. Besides, the mechanism of quinoline was similarly, which processed a [3 + 2 + 1] annulation through Cu(II)-mediated aerobic oxidation.

Conclusion

The 1,2,4-oxadiazole and quinazoline scaffold are two critical nitrogen-containing heterocycles, however there is no general synthesis strategy for these two heterocyclic scaffolds under a similar reaction condition. Herein, we first report analogous three-component cascade synthesis strategy for substituted 1,2,4-oxadiazole and quinazoline derivatives synthesis from readily available benzaldehyde, benzylamine and hydroxylamine or aniline. Both of the reaction sequences contain nucleophilic addition of C–N bond, introduce a halogen donor, nucleophilic substitution and Cu(II)-catalyzed aerobic oxidation. The building of 1,2,4-oxadiazole and quinazoline possess [2 + 2 + 1] annulation and [3 + 2 + 1] annulation *via* a Cu(II)-catalyzed dehydrogenative cyclization respectively, which demonstrated good yields, broad substrate scope and oxygen as a green oxidant. This protocol provides efficient approach to 1,2,4-oxadiazole and quinazoline derivatives.

Experimental Section

General Procedure for the Synthesis of Oxadiazole (4 a)

Benzaldehyde **1** (0.5 mmol, 1.0 equiv.), benzylamine **2** (0.5 mmol, 1.0 equiv.), hydroxylamine **3** (0.5 mmol, 1.0 equiv.), $CuBr_2$ (10 mmol%), 1,10-phenanthroline (20 mmol%), DBH (0.5 mmol, 1.0 equiv.), Et_3N (0.5 mmol, 1.0 equiv.) were added into the EtOH (4 mL), the mixture was stirred at 80 °C under O_2 for 8 h. Then the mixture was cooled to room temperature, and the reaction mixture was diluted with water, extracted with ethyl acetate (10 mL*3). The organic solvent was washed with brine, dried by anhydrous Na_2SO_4 and concentrated to give the crude product. The crude product was purified by flash column chromatography on silica gel (PE/EA = 100:1).

General Procedure for the Synthesis of Quinazoline (6 a)

Benzaldehyde **1** (0.5 mmol, 1.0 equiv.), benzylamine **2** (0.5 mmol, 1.0 equiv.), aniline **5** (0.5 mmol, 1.0 equiv.), $CuBr_2$ (10 mmol%), 1,10-phenanthroline (20 mmol%), DBH (0.5 mmol, 1.0 equiv.), and Et_3N (0.5 mmol, 1.0 equiv.) were added into the toluene (4 mL), the mixture was stirred at 100 °C under O_2 for 14 h. Then the reaction mixture was cooled to room temperature, and the mixture was diluted with water, extracted with ethyl acetate (10 mL *3). The organic layer was washed with a brine, dried by anhydrous Na_2SO_4 and concentrated to give the crude product. The crude product was purified by flash column chromatography on silica gel (PE/EA = 80:1)

Acknowledgements

We gratefully acknowledge the National Science Foundation of China (No. 81573304, 81703342), Natural Science Foundation of Jiangsu (No. BK20161050), Natural Science Foundation of Nanjing University of Chinese Medicine (No. NZY81703342).

References

[1] For selected examples, see: a) K. Biernacki, M. Daśko, O. Ciupak, K. Kubiński, J. Rachon, S. Demkowicz, *Pharmaceuticals.* **2020**, *13*, doi: 10.3390/ph13060111; b) L. L. Xu, J. F. Zhu, X. L. Xu, J. Zhu, L. Li, M. Y. Xi, Z. Y. Jiang, M. Y. Zhang, F. Liu, M. C. Lu, Q. C. Bao, C. Zhang, J. L. Wei, X. J. Zhang, Q. D. You, H. P. Sun, *J. Med. Chem.* **2015**, *58*, 5419–5436; c) S. Moniot, M. Forgione, A. Lucidi, G. S. Hailu, A. Nebbioso, V. Carafa, F. Baratta, L. Altucci, N. Giacche, D. Passeri, R. Pellicciari, A. Mai, C. Steegborn, *J. Med. Chem.* **2017**, *60*, 2344–2360; d) M. E. Layton, M. J. Kelly, K. J. Rodzinak, P. E. Sanderson, S. D. Young, R. A. Bednar, A. G. DiLella, T. P. Mcdonald, H. Wang, S. D. Mosser, J. F. Fay, M. E. Cunningham, D. R. Reiss, C. Fandozzi, N. Trainor, A. N. Liang, E. V. Lis, G. R. Seabrook, M. O.

Urban, J. Yergey, K. S. Koblan, *ACS Chem. Neurosci.* **2011**, *2*, 352–362.

[2] For selected examples, see: a) Ž. Jakopin, *Tetrahedron Lett.* **2018**, *59*, 4320–4322; b) M. Guerrero, M. Urbano, E. K. Kim, A. Gamo, S. Riley, L. Abgaryan, N. Leaf, L. J. V. Orden, S. J. Brown, J. Y. Xie, F. Porreca, M. D. Cameron, H. Rosen, *J. Med. Chem.* **2019**, *62*, 1761–1780; c) L. Aurelio, C. M. Pitman, A. Sexton, V. Oliver, L. Davies, R. Rebello, L. Furic, D. J. Creek, S. Pitson, B. L. Flynn, *J. Med. Chem.* **2016**, *59*, 965–984.

[3] For selected examples, see: a) E. M. Welch, E. R. Barton, J. Zhuo, Y. Tomizawa, W. J. Friesen, P. Trifillis, S. Paushkin, M. Patel, C. R. Trotta, S. Hwang, R.-G. Wilde, G. Karp, J. Takasugi, G. Chen, S. Jones, H. Ren, Y. C. Moon, D. Corson, A. A. Turpoff, J. A. Campbell, M. M. Conn, A. Khan, N. G. Almstead, J. Hedrick, A. Mollin, N. Risher, M. Weetall, S. Yeh, A. A. Branstrom, J. M. Colacino, J. Babiak, W. D. Ju, S. Hirawat, V. J. Northcutt, L. L. Miller, P. Spatrick, F. He, M. Kawana, H. Feng, A. Jacobson, S. W. Peltz, H. L. Sweeney, *Nature* **2007**, *447*, 87; b) J. Berger, M. Li, S. Berger, M. Meilak, J. Rientjes, P. D. Currie, *J. Cell. Mol. Med.* **2020**, *24*, 6680–6689.

[4] For selected examples, see: a) M. S. Raghu, C. B. P. Kumar, K. Y. Kumar, M. K. Prashanth, B. K. Jayanna, *J. Heterocycl. Chem.* **2019**, *56*, 2046–2051; b) F. Z. Jiang, S. Jun, L. Na, D. M. Han, B. X. Ping, *J. Agric. Food Chem.* **2019**, *67*, 11598–11606; c) T. S. Patel, J. D. Bhatt, R. B. Dixit, C. J. Chudasama, B. D. Patel, B. C. Dixit, *Bio. Med. Chem.* **2019**, *27*, 3574–3586; d) H. Georgey, N. Abdel-Gawad, S. Abbas, *Molecules* **2008**, *13*, 2557–2569; e) D. Xie, J. Shi, A. Zhang, Z. Lei, G. C. Zu, Y. Fu, X. H. Gan, L. Yin, B. Song, D. Y. Hu, *Bio. Chem.* **2018**, *80*, 433; f) J. Peng, T. Lin, W. Wang, Z. Xin, T. Zhu, Q. Gu, D. Li, *J. Nat. Prod.* **2013**, *76*, 1133–1140; g) I. Khan, A. Ibrar, W. Ahmed, A. Saeed, *Eur. J. Med. Chem.* **2014**, *90*, 124–169; h) J. Jamroskovic, M. Doimo, K. Chand, I. Obi, R. Kumar, K. Brannstrom, M. Hedenström, R. N. Das, A. Akhunzianov, M. Deiana, K. Kasho, S. S. Sato, P. L. Pourbozorgi, J. E. Mason, P. Medini, D. Öhlund, S. Wanrooij, E. Chorell, N. Sabouri, *J. Am. Chem. Soc.* **2020**, *142*, 2876–2888.

[5] M. H. Cohen, J. R. Johnson, Y. F. Chen, R. Sridhara, R. Pazdur, *Oncologist* **2005**, *10*, 461.

[6] For selected examples, see: a) A. Sauer, L. Wolf, N. Quoos, M. B. Rodrigues, A. L. Braga, O. E. D. Rodrigues, L. Dornelles, *J. Org. Chem.* **2019** (Article ID: 8589325); b) D. Suresh, K. Kanagaraj, K. Pitchumani, *Tetrahedron Lett.* **2014**, *55*, 3678–3682; c) B. Kaboudin, L. Malekzadeh, *Tetrahedron Lett.* **2011**, *52*, 6424–6426; d) B. Kaboudin, F. Saadati, *Tetrahedron Lett.* **2007**, *48*, 2829–2832; e) J. J. Lade, B. N. Patil, K. S. Vadagaonkar, A. C. Chaskar, *Tetrahedron Lett.* **2017**, *58*, 2103–2108; f) P. D. Parker, J. G. Pierce, *Synthesis.* **2016**, *48*, 1902–1909; g) F. Zhang, Y. Wang, S. Chiba, *Org. Biomol. Chem.* **2013**, *11*, 6003–6007.

[7] For selected examples, see: a) V. Mercalli, A. Massarotti, M. Varese, M. Giustiniano, F. Meneghetti, E. Novellino, G. C. Tron, *J. Org. Chem.* **2015**, *80*, 9652–9661; b) X. Wang, J. P. Fu, J. X. Xie, Q. H. Teng, H. T. Tang, Y. M. Pan, *Org. Biomol. Chem.* **2020**, *18*, 4936–4940; c) M. R. Kuram, W. G. Kim, K. Myung, S. Y. Hong, *Eur. J. Org. Chem.* **2016**, 438–442.

[8] For selected examples, see: a) Y. X. Tang, G. H. Imler, D. A. Parrish, J. M. Shreeve, *Org. Lett.* **2018**, *20*, 8039–8042; b) E. Li, M. Wang, Z. Wang, W. Q. Yu, J. B. Chang, *Tetrahedron* **2018**, *74*, 4613–4618.

[9] Q. L. Bian, C. L. Wu, J. P. Yuan, Z. D. Shi, T. Ding, Y. W. Huang, H. Xu, Y. Q. Xu, *J. Org. Chem.* **2020**, *85*, 4058–4066.

[10] For selected examples, see: a) Z. H. Zhang, X. N. Zhang, L. P. Mo, Y. X. Li, F. P. Ma, *Green Chem.* **2012**, *14*, 1502–1063; b) Y. Yan, Y. Zhang, C. Feng, Z. Zha, Z. Wang, *Angew. Chem. Int. Ed.* **2012**, *124*, 8201–8205; c) J. Zhang, C. Yu, S. Wang, C. Wan, Z. Wang, *Chem. Commun.* **2010**, *46*, 5244–5246; d) P. T. K. Arachchige, C. S. Yi, *Org. Lett.* **2019**, *21*, 3337–3341; e) C. U. Maheswari, G. S. Kumar, M. Venkateshwar, R. A. Kumar, M. L. Kantam, K. R. Reddy, *Adv. Synth. Catal.* **2010**, *352*, 341–346; f) T. Chatterjee, D. Kim, E. J. Cho, *J. Org. Chem.* **2018**, *83*, 7423–7430; g) M. Ramanathan, Y. H. Liu, S. M. Peng, S. T. Liu, *Org. Lett.* **2017**, *19*, 5840–5843; h) K. Hu, Q. Q. Zhen, J. L. Gong, T. X. Cheng, L. J. Qi, Y. L. Shao, J. X. Chen, *Org. Lett.* **2018**, *20*, 3083–3087.

[11] For selected examples, see: a) J. P. Lin, F. H. Zhang, Y. Q. Long, *Org. Lett.* **2014**, *16*, 2822–2825; b) Z. G. Lv, B. N. Wang, Z. Y. Hu, Y. M. Zhou, W. Q. Yu, J. B. Chang, *J. Org. Chem.* **2016**, *81*, 9924–9930; c) L. Xu, H. Li, Z. Liao, K. Lou, H. Xie, H. Li, W. Wang, *Org. Lett.* **2015**, *17*, 3434–3437.

[12] For selected examples, see: a) Y. Lv, Y. Li, T. Xiong, W. Pu, H. Zhang, K. Sun, Q. Liu, Q. Zhang, *Chem. Commun.* **2013**, *49*, 6439–6441; b) W. Zhang, F. Guo, F. Wang, N. Zhao, L. Liu, J. Li, Z. Wang, *Org. Biomol. Chem.* **2014**, *12* 5752–5756; c) X. Cheng, H. Wang, F. Xiao, G. J. Deng, *Green Chem.* **2016**, *18*, 5773–5776; d) Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2010**, *12*, 3963–3965.

[13] Y. J. Sun, H. M. Sun, Y. Wang, F. Xie, *Org. Lett.* **2020**, *22*, 6756–6759.

[14] The principles of green and sustainable chemistry: a) R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437–1451; b) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283.

[15] For selected examples, see: a) J. H. Kim, S. Greβies, F. Glorius, *Angew. Chem. Int. Ed.* **2016**, *128*, 5667–5671; b) Q. Q. Lu, S. Greβies, S. Cembellín, F. J. R. Klauck, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *129*, 12954–12958.

[16] For selected examples, see: a) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey, *J. Am. Chem. Soc.* **2007**, *129*, 7500–7501; b) J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim, S. Chang, *J. Am. Chem. Soc.* **2012**, *134*, 9110–9113; c) E. N. Bess, R. J. DeLuca, D. J. Tindall, M. S. Oderinde, J. L. Roizen, J. D. Bois, M. S. Sigman, *J. Am. Chem. Soc.* **2014**, *136*, 5783–57889; d) S. H.

Park, J. Kwak, K. Shin, J. Ryu, Y. Park, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 2492–2502; e) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040–1052; f) A. Das, A. G. Maher, J. Telse, D. C. Powers, *J. Am. Chem. Soc.* **2018**, *140*, 10412–10416; g) T. Gogula, J. Q. Zhang, H. B. Zou, *Org. Lett.* **2019**, *21*, 5933–5937; h) S. Samanta, S. Mondal, D. Ghosh, A. Hajra, *Org. Lett.* **2019**, *21*, 4905–4909; i) X. Wang, J. Zhang, D. Chen, B. Wang, X. Yang, Y. Ma, M. Szostak, *Org. Lett.* **2019**, *21*, 7038–7043.

[17] Y. Yang, W. B. Dong, Y. S. Guo, R. M. Rioux, *Green Chem.* **2013**, *15*, 3170–3175.

[18] For selected examples, see: a) G. Liu, G. Yin, L. Wu, *Angew. Chem. Int. Ed.* **2008**, *120* 4811–4814; b) K. H. Ng, A. S. C. Chan, W. Y. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12862–12864; c) B. Xiao, T. J. Gong, J. Xu, Z. J. Liu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1466–1474; d) E. J. Yoo, S. Ma, T. S. Mei, K. S. L. Chan, J. Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7652–7655; e) Z. Dong, G. Dong, *J. Am. Chem. Soc.* **2013**, *135*, 18350–18355; f) P. Wang, G. Li, P. Jain, M. E. Farmer, J. He, P. Shen, J. Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14092–14099; g) B. S. Zhang, Y. Li, Z. Zhang, Y. An, Y. H. Wen, X. Y. Gou, S. Q. Quan, X. G. Wang, Y. M. Liang, *J. Am. Chem. Soc.* **2019**, *141*, 9731–9738.

[19] S. S. Stahl, *Science* **2005**, *309*, 1824–1826.

[20] For some selected examples about copper-catalyzed reactions using molecular oxygen as oxidant in recent years, see: a) Y. Yang, W. Dong, Y. Guo, R. M. Rioux, *Green Chem.* **2013**, *15*, 3170–3175; b) H. He, Z. Wang, W. Bao, *Adv. Synth. Catal.* **2010**, *352*, 2905–2912; c) S. Guo, -B. Qian, Y. Xie, C. Xia, H. Huang, *Org. Lett.* **2011**, *13*, 522–525; d) J. Jover, F. Maseras, *Chem. Commun.* **2013**, *49*, 10486–10488; e) K. V. N. Esguerra, Y. Fall, L. Petitjean, J. P. Lumb, *J. Am. Chem. Soc.* **2014**, *136*, 7662–7668; f) C. Y. Liu, Y. Li, J. Y. Ding, D. W. Dong, F. S. Han, *Chem. Eur. J.* **2014**, *20*, 2373–2379; g) Q. Wu, Y. Luo, A. Lei, J. You, *J. Am. Chem. Soc.* **2016**, *138*, 2885–2888.

[21] B. Xu, E. M. Hartigan, G. Feula, Z. Huang, J. P. Lumb, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2016**, *55*, 15802–15806.

[22] For selected examples, see: a) W. Guo, J. Liao, D. Liu, J. Li, F. Ji, W. Wu, H. Jiang, *Angew. Chem. Int. Ed.* **2017**, *56*, 1289–1293; b) H. Chen, S. Sanjaya, Y. F. Wang, S. Chiba, *Org. Lett.* **2013**, *15*, 212–215; c) X. Y. Wang, X. Qiu, J. L. Wei, J. Z. Liu, S. Song, W. Wang, N. Jiao, *Org. Lett.* **2018**, *20*, 2632–2636; d) A. E. Wendlandt, S. S. Stahl, *J. Am. Chem. Soc.* **2014**, *136*, 11910–11913.

FULL PAPER

Copper-Catalyzed Three-Component Cascade Reaction of Benzaldehyde with Benzylamine and Hydroxylamine or Aniline: Synthesis of 1,2,4-Oxadiazoles and Quinazolines

Adv. Synth. Catal. **2021**, *363*, 1 – 10

C. Wang, X. Rui, D. Si, R. Dai, Y. Zhu, H. Wen, W. Li*, J. Liu*