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Copper-catalyzed three-component reaction of *N*-heteroaryl aldehydes, nitriles, and water

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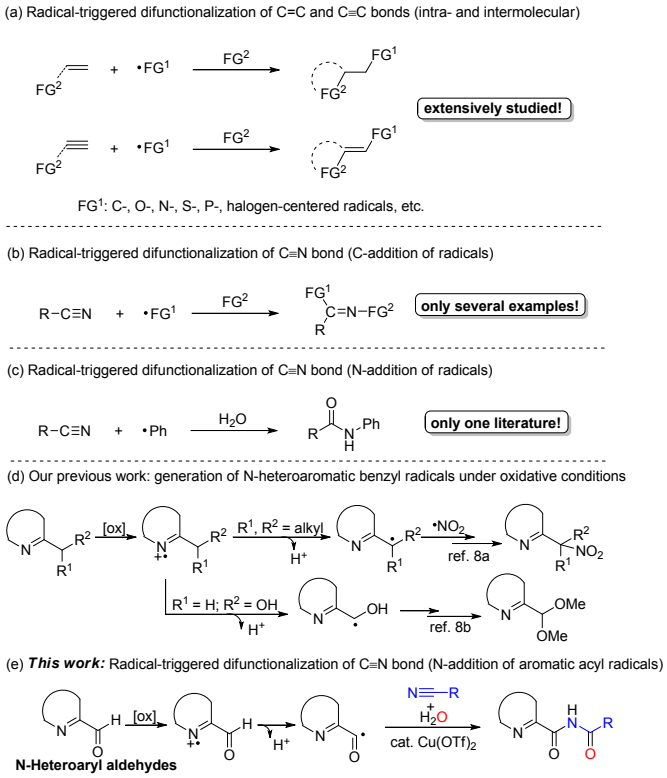
An efficient and straightforward method for the synthesis of *N*-heteroaroyl imides has been successfully developed involving a copper-catalyzed radical-triggered three-component reaction of *N*-heteroaryl aldehydes, nitriles, and water. Mechanistic studies indicate that the reaction may undergo a radical-triggered Ritter-type reaction in which water serves as the oxygen source for the C-O bond. The reaction has advantages of broad substrate scope for the *N*-heteroaryl aldehydes, atom economy, and simple operation.

Introduction

In the past few decades, the radical-triggered inter- and intramolecular difunctionalizations of the C=C or C≡C bonds have received considerable attention because such reactions usually provide a highly efficient strategy for the construction of complex molecules in a simple operation and step-economy manner.[1-4] Up to now, a variety of C-C/C-C, C-C/C-X, or even C-X/C-X′ (X, X′ = heteroatoms) structural units can be efficiently constructed from the C=C or C≡C moieties based on various carbon-centered or heteroatom-centered radical species (Scheme 1a).[1-4]

The C≡N bond, structurally similar to the C=C and C≡C bond, is also a useful and versatile building block in various organic transformations.[5-7] As far as the difunctionalization of the C≡N bond is concerned, a lot of examples have been reported in recent years.[6,7] However, among them, examples involving the radical-triggered difunctionalizations are still limited in comparison with those examples in domains of the C=C and C≡C bond (Scheme 1b).[7] Among these limited examples, the Malacria's group reported an AIBN/*n*-Bu_3SnH-mediated radical cascade cyclization of *N*-(2-iodobenzyl)-*N*-acylcyanamides to construct tetracyclic quinazolinones.[7a,b] Later, Yu and co-workers further realized the same reaction by employing photoredox strategy to initiate radicals.[7c] In recent years, Sun's group developed a convenient approach to prepare phenanthridine derivatives involving several photocatalyst-induced radical cascade reactions of *N*-(2-cyanoaryl)acrylamides.[7d-f] All the aforementioned radical-triggered difunctionalizations of the C≡N bond proceed through the addition of radical species to the carbon atom of the cyano group as the initial step, while the radical-triggered direct *N*-addition reactions are relatively rare. To the best of our knowledge, there only one literature has been reported on this type of reaction, which involves an *N*-addition of phenyl radicals



Scheme 1 The radical-triggered difunctionalization of the C=C, C≡C, and C≡N bonds.

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Electronic Supplementary Information (ESI) available: General reaction procedures, characterization data, mechanic experiments, and copies of NMR spectra. See DOI: 10.1039/x0xx00000x

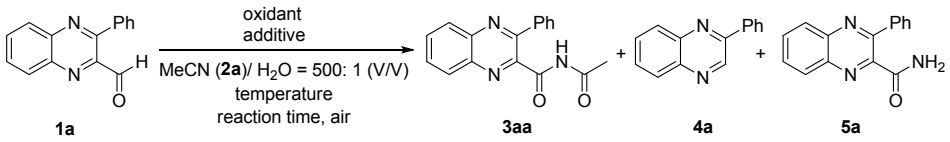
to the C≡N bond leading to the synthesis of *N*-phenyl amides (Scheme 1c).[7g] From the synthetic point of view, it is still highly desirable to develop efficient methods for the construction of molecule diversity via the difunctionalization of the C≡N bond involving the radical-triggered direct *N*-addition reactions.

In our previous work, we disclosed that *N*-heteroaromatics having a benzyl C-H bond at the α-position to the *N*-atom in *N*-heteroaromatics may easily generate *N*-heteroaromatic benzyl radicals under oxidative conditions, which may further undergo radical tandem reactions (Scheme 1d).[8] On the basis of this founding, we envision that *N*-heteroaryl aldehydes might similarly generate *N*-heteroaromatic acyl radicals under oxidative conditions (Scheme 1e). As part of our ongoing research interests in radical reactions[8] and copper-catalyzed efficient tandem reactions,[9,10] we herein describe a copper-catalyzed three-component reaction[11] of *N*-heteroaryl aldehydes, nitriles, and water for the preparation of *N*-heteroaroyl imides involving a radical-triggered direct *N*-addition as the key step (Scheme 1e).

In view of the potential application of quinoxaline derivatives in chemical, pharmaceutical, and materials science fields,[12] our study commenced with the three-component reaction of 3-phenylquinoxaline-2-carbaldehyde (**1a**), acetonitrile (**2a**), and water as the model reaction for the optimization of the reaction conditions (Table 1). When **1a** was treated with NCS (2.0 equiv) in acetonitrile-water media (500/1, V/V) at 100 °C for 18 h, *N*-acetyl-3-phenylquinoxaline-2-carboxamide **3aa** was obtained in 38% yield along with the formation of **4a** and **5a** as side products (entry 1, Table 1). Among several oxidants screened, $K_2S_2O_8$ showed the most effectiveness for the formation of **3aa** (entry 2 vs 1, 3, and 4, Table 1). It was found that decreasing the amount of $K_2S_2O_8$ resulted in a low yield of **3aa** (entry 5, Table 1), and none of **3aa** was obtained in the absence of $K_2S_2O_8$ (entry 6, Table 1). In order to further improve the yield of **3aa**, a series of copper salts were screened as additives (entries 7-10, Table 1). Gratifyingly, when $Cu(OTf)_2$ (20 mol %) was added, the reaction could afford **3aa** in 79% yield even with a less consumption of $K_2S_2O_8$

Results and discussion

Table 1 Optimization of the reaction conditions[a]



Entry	Copper salt (mol %)	Oxidant (equiv)	Temp (°C)	Time (h)	Yield (%)[b] 3aa/4a/5a
1	--	NCS (2.0)	100	18	38/6/17
2	--	$K_2S_2O_8$ (2.0)	100	18	63/12/28
3	--	$(NH_4)_2S_2O_8$ (2.0)	100	18	59/10/23
4	--	TBHP (2.0)	100	18	34/40/trace
5	--	$K_2S_2O_8$ (1.0)	100	18	39/trace/11
6	--	--	100	18	N.R.
7	$Cu(OTf)_2$ (20)	$K_2S_2O_8$ (1.0)	60	6	79/trace/10
8	$CuCl_2$ (20)	$K_2S_2O_8$ (1.0)	60	6	39/trace/10
9	$Cu(acac)_2$ (20)	$K_2S_2O_8$ (1.0)	60	6	--/--/--
10	$Cu(OAc)_2$ (20)	$K_2S_2O_8$ (1.0)	60	6	15/--/--
11	--	$K_2S_2O_8$ (1.0)	60	6	23/--/--
12	$Cu(OTf)_2$ (10)	$K_2S_2O_8$ (1.0)	60	6	66/trace/trace
13	$Cu(OTf)_2$ (5)	$K_2S_2O_8$ (1.0)	60	6	63/trace/trace
14	$Cu(OTf)_2$ (20)	TBHP (2.0)	60	6	47/13/trace
15	**$Cu(OTf)_2$ (20)**	**$(NH_4)_2S_2O_8$ (1.0)**	60	6	**87/trace/trace**
16	$Cu(OTf)_2$ (20)	$PhI(OAc)_2$ (1.0)	60	6	18/--/--
17	$Cu(OTf)_2$ (20)	$(NH_4)_2S_2O_8$ (1.2)	60	6	85/trace/trace
18	$Cu(OTf)_2$ (20)	$(NH_4)_2S_2O_8$ (0.8)	60	6	82/trace/trace
19	$Cu(OTf)_2$ (20)	$(NH_4)_2S_2O_8$ (1.0)	60	6	85/trace/trace
20	$Cu(OTf)_2$ (20)	$(NH_4)_2S_2O_8$ (1.0)	60	6	75/trace/14
21	$Cu(OTf)_2$ (20)	$(NH_4)_2S_2O_8$ (1.0)	60	6	53/trace/19

[a]Reaction conditions: **1a** (0.3 mmol), additive (n mol % based on **1a**), oxidant (m equiv based on **1a**), $MeCN/H_2O$ = 500:1 (V/V, 3.0 mL), at T °C unless otherwise noted. [b]Isolated yield. [c]Solvent: $MeCN/H_2O$ = 250:1 (V/V, 3.0 mL). [d]Solvent: $MeCN/H_2O$ = 100:1 (V/V, 3.0 mL). [e]Solvent: $MeCN/H_2O$ = 50:1 (V/V, 3.0 mL).

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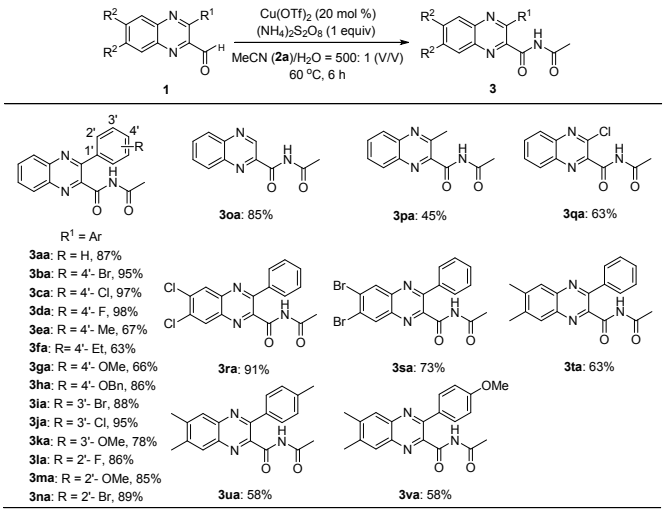
(1.0 equiv), with a shorter reaction time (6 h), and under a lower temperature (60 °C) (entry 7 vs 2, Table 1). Note that the use of 20 mol % of $Cu(OTf)_2$ was necessary to get a satisfactory yield of **3aa** (entries 11-13 vs 7, Table 1). In the case of $Cu(OTf)_2$ as an additive, the reaction could give an even better yield of **3aa** when $(NH_4)_2S_2O_8$ was used as the oxidant instead of $K_2S_2O_8$ (entry 15 vs 7, Table 1). Either increasing or decreasing the amount of $(NH_4)_2S_2O_8$ resulted in a lower yield of **3aa** (entries 17-18, Table 1). Finally, the influence of water content on the reaction was also evaluated by the extra addition of water into the reaction mixture. Unfortunately, decreased yields of **3aa** were obtained which suggested a subtle reaction condition requiring an existence of trace amount of water in this reaction system (entries 19-21 vs 15, Table 1).

Under the established reaction conditions, the scope of quinoxaline-2-carbaldehydes **1** was investigated (Table 2). We first examined the generality of **1** with various aryl groups at the 3-position of the quinoxaline scaffold (R^1 = Ar, **3aa-na** and **3ra-va**, Table 2). As seen from Table 2, quinoxaline-2-carbaldehydes **1** containing a range of aryl rings with various substitution patterns (*para*-, *meta*- or *ortho*-) were able to undergo the three-component reaction and the desired products could be obtained in moderate to excellent yields (**3ba-ha** and **3ra-va**, Table 2). Generally, substrates **1** bearing electron-deficient phenyl rings reacted more smoothly and delivered higher yields of products than those possessing electron-rich ones (**3ba-da** vs **3ea-ha**; **3ia**, **3ja** vs **3ka**, Table 2). In addition, substrates with R^1 as non-aryl groups (for example, R^1 = H, Me, or Cl) were also workable for the reaction albeit in lower yields of products in several cases (**3pa**, **3qa**, Table 2). Furthermore, quinoxaline-2-carbaldehydes with different R^2 groups including Cl, Br, and methyl were also investigated, in which cases the desired products could be obtained in moderate to good yields (**3ra**-**va**, Table 2). A 3 mmol-scale

Table 2 Substrate scope of quinoxaline-2-carbaldehydes **1**.[a]



[a]Reaction conditions: **1** (0.3 mmol), $Cu(OTf)_2$ (20 mol % based on **1**), $(NH_4)_2S_2O_8$ (1.0 equiv), $MeCN/H_2O$ = 500:1 (V/V, 3.0 mL), at 60 ºC for 6 h unless otherwise noted.

synthesis of **3aa** was also investigated, and **3aa** could be obtained in 70% yield (see eq. *1S* in ESI). A dialdehyde (quinoxaline-2,3-dicarbaldehyde **1w**) was used to react with acetonitrile and water under the optimal conditions. Unexpectedly, a concomitant deformylation also occurred and imide **3oa** was obtained in 65% yield.

Next, the scope of different nitriles **2** was investigated by reacting with quinoxaline-2-carbaldehyde **1a** under the optimized reaction conditions (Table 3). It was found that the yield of the desired imides depended heavily on the structure of nitriles. For instance, *n*-butyronitrile, *iso*-butyronitrile, benzonitrile, or 4-methoxybenzonitrile reacted with **1a** and water smoothly, and the desired products could be obtained in moderate to good yields (54-83%, **3ab**, **3ac**, **3af**, **3ag,** Table 3). In contrast, 3-methoxypropionitrile, acrylonitrile or 4-nitrobenzonitrile gave a much lower yields of the products (**3ad**, **3ae**, **3ah**, Table 3). An attempt to use a stoichiometric amount of benzonitrile for the reaction was also carried out by using the DCE-water mixture as the solvent, and the reaction could still afford **3af** in 51% yield albeit in a prolonged reaction time.

Table 3 Substrate scope of nitriles.[a]

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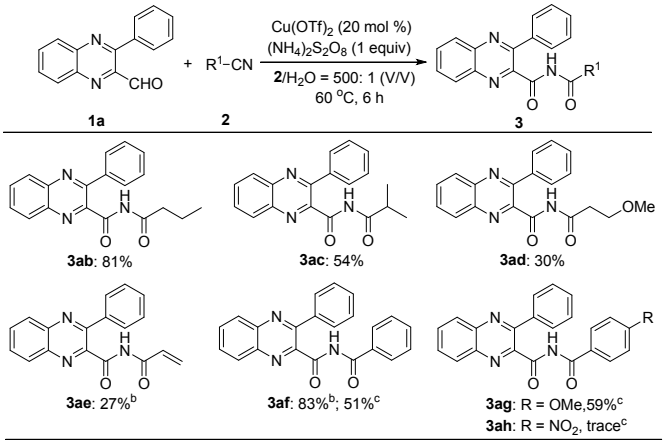
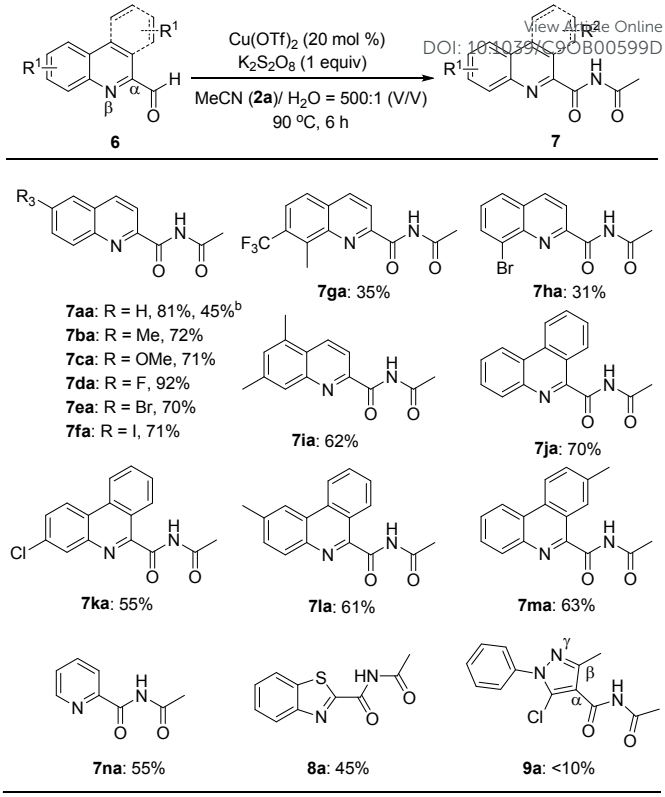


[a]Reaction conditions: **1a** (0.3 mmol), **2**/ H_2O = 500:1 (V/V, 3.0 mL), $Cu(OTf)_2$ (20 mol % based on **1a**), $(NH_4)_2S_2O_8$ (0.3 mmol), at 60 ºC for 6 h unless otherwise noted. [b]The reaction was carried out in 90 °C, and the reaction time was 12 h. [c]Reaction conditions: **1a** (0.3 mmol), **2f-h** (3.0 equiv based on **1a**), $Cu(OTf)_2$ (20 mol % based on **1a**), $(NH_4)_2S_2O_8$ (1.0 equiv based on **1a**) in 1,2-dichloroethane at 100 ºC for 18 h.

To make the reaction synthetically valuable, we further set out to investigate the scope of different *N*-heteroaryl benzaldehydes **6** by treatment of **6** with acetonitrile **2a** and water (Table 4). First, a range of quinoline-2-carbaldehydes were investigated. Note that in these cases $K_2S_2O_8$ is a more suitable oxidant and 90 °C is a more suitable temperature for getting a satisfactory yield of the target product. Under the modified reaction conditions, a series of substituted quinoline-2-carbaldehydes underwent the three-component reaction smoothly to furnish the corresponding *N*-acetyl-quinoline-2-carboxamide in synthetically acceptable yields (**7aa**-**ia**, Table 4). Next, phenanthridine-6-carbaldehydes were also proven to be suitable substrates for the present reaction and the desired imides could be obtained in moderate yields (**7ja**-**ma**, Table 4). When 2-pincolinaldehyde was used, the desired product **7na** was obtained in 55%. In addition, a benzo[*d*]thiazole-2-carbaldehyde (**8**) was able to convert into the desired imide in 45% yield (**8a**, Table 4). Finally, a pyrazole-4-carbaldehyde (**9**) having a γ-N to the formyl group was tested for the reaction. Unfortunately, the reaction afforded the desired product in only lower than 10% yield (**9a**, Table 4).

Table 4 Substrate Scope of Other *N*-Heteroaryl Aldehydes **6**.[a]



[a]Reaction conditions: **6** (0.3 mmol), $Cu(OTf)_2$ (20 mol % based on **6**), $K_2S_2O_8$ (0.3 mmol), MeCN (**2a**)/H_2O = 500:1 (V/V, 3.0 mL), at 90 ºC for 6 h unless otherwise noted. [b]$(NH_4)_2S_2O_8$ (1.0 equiv) was used at 90 °C.

To gain insight into the mechanism of the present three-component reaction, several mechanistic experiments were carried out (Scheme 2). First, isotope labeling experiment was conducted to figure out the oxygen source for the product formation. H_2O^{18} was added to the model reaction in anhydrous acetonitrile under the nitrogen atmosphere (Scheme 2a). To our expectation, the ^{18}O-incorporated product **3aa-O^{18}** was detected by LRMS analysis, which suggested that water served as the oxygen source for the formation of the C-O bond in **3aa** (see in the ESI). Next, a radical scavenger (TEMPO or BHT) was subjected to the standard reaction conditions. As a result, the reaction was thoroughly suppressed by employing 2.0 equivalents of TEMPO (Scheme 2b); a similar result was obtained from the reaction using BHT (butylated hydroxytoluene) as a radical scavenger (Scheme 2c). These results supported that a radical process might be involved in this reaction.[13] Furthermore, a competitive reaction between **1a** and **1a**-*d* (96%-D enrichment) for the measurement of intermolecular KIE was carried out (Scheme 2d). The intermolecular k_H/k_D of **1a** to **1a**-*d* was calculated to be 1.0 (Figure *S2* in the Supporting Information), suggesting that the cleavage of the C-H bond is not the rate-determining step. Finally, quinoline-3-carbaldehyde **10**, benzaldehyde **11**, or butyraldehyde **12** was investigated for the reaction (Scheme 2e). Unfortunately, these substrates failed to give the desired products while the starting materials were almost recovered. These results suggest that substrates containing an N-atom at

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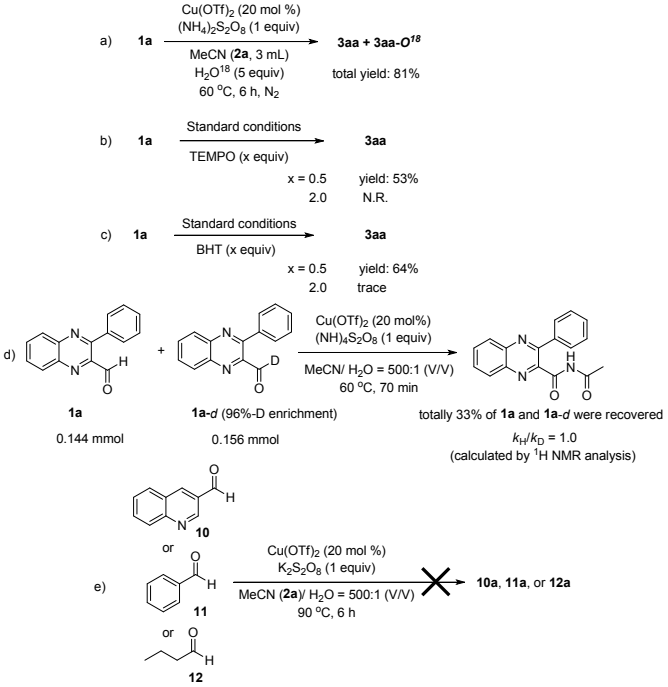
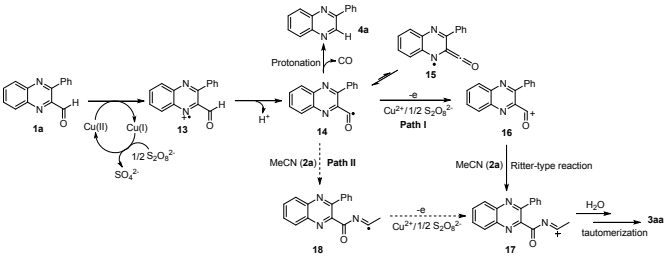
the β-position of the formyl group are very essential for the reaction.



Scheme 2 Mechanistic experiments.

On the basis of the above experiments and previous literature,[7g,8,14-19] a proposed mechanism for the radical-triggered three-component reaction of **1a**, **2a**, and water is described in Scheme 3. Initially, **1a** might be oxidized into intermediate **13** by the Cu(II)/$S_2O_8^{2-}$ system through a single-electron-tranfer process (SET).[8,14] **13** released a proton to form acyl radical species **14**.[8] Then the oxidation of **14** via a SET process followed by the *N*-addition of the resulting acyl cation species **16** to **2a** leading to intermediate **17**.[14-16] The cationic intermediate **17** was trapped by water followed by a tautomerization to give the final product **3aa** (Path I).[15,16] In addition, a mechanism involved in first *N*-addition of **14** to the C≡N triple bond of **1a** followed by the formation of intermediate **17** might be also possible (Path II).[7g,14,17,18]



Scheme 3 Proposed mechanism for the formation of **3aa**.

Conclusions

In summary, a copper-catalyzed radical-triggered Ritter-type reaction has been achieved in a three-component reaction of *N*-heteroaryl aldehydes, nitriles and water in the presence of persulfate salts. Thus a variety of *N*-(hetero)aroyl-containing imides could be prepared in moderate to excellent yield under simple reaction conditions. Mechanistic studies indicated that the formation of *N*-(hetero)aromatic acyl radicals is the key step for the present three-component reaction.

Experimental

General experimental methods

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without purification. Melting points were uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a spectrometer at 25 °C in $CDCl_3$ at 500 MHz and 125 MHz (or at 400 MHz and 100 MHz), respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Chemical shifts of ^{13}C NMR were reported relative to the solvent signal ($CDCl_3$: δ = 77.16 ppm). GC-MS experiments were performed with EI source; high resolution mass spectra (HRMS) were obtained on a TOF MS instrument with EI or ESI source. Acetonitrile is dehydrated by CaH_2 before preparation of the combined MeCN/H_2O solvent system. Flash column chromatography was performed on silica gel (100-200 mesh) with the indicated solvent mixtures.

Preparation of quinoxaline-2-carbaldehydes 1, quinoline-2-carbaldehydes (6a-i), phenanthridine-6-carbaldehydes (6j-m), 8, and 9

All quinoxaline-2-carbaldehydes (**1**) and **8** were synthesized according to the reported literature.[8b] Substrates **1a**-**1e**,[8b] **1g**,[8b] **1k**,[8b] **1m**,[8b] **1o**,[8b] **1p**,[19] **1r**,[8b] **1t**,[8b] **1v**,[8b] and **8**[8b] are known compounds and their NMR spectra were consistent with those reported data. Quinoline-2-carbaldehydes (**6a-i**) and phenanthridine-6-carbaldehydes (**6j-m**) were synthesized from the oxidation of corresponding 2-methylquinoline and 6-methyl phenanthridine with SeO_2 according to the literature procedure.[20,21] For a typical procedure: 2-methylquinoline **19** (1.4 g, 10 mmol), selenium dioxide (2.0 g, 18 mmol) was added to a mixture of dioxane (80 mL) and H_2O (5 mL) and the mixture was stirred and heated to reflux for 5 h. Upon completion, the solvent was removed under vacuum. Then the residue was dissolved in CH_2Cl_2 (80 mL), and filtered through Celite. The filtrate extracted with H_2O (80 mL) for three times to remove redundant selenium dioxide and the organic phase was collected. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100-200 mesh) using petroleum ether-EtOAc (20:1-6:1) as eluent to give pure **6a** (1.3g, 80%). Substrates **6a**-**6d**,[21a] **6e**,[21b] **6f**,[21c] **6h**,[21d] **6j**[22] are known compounds and their NMR spectra were consistent with those reported data. **9** was synthesized according to the reported procedure, and its spectra were consistent with the reported one.[24] Substrates **1w**, **10**-**12** are commercially available.

Typical experimental procedure for the synthesis of *N*-acetyl-quinoxaline-2-carboxamides 3

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1 (0.3 mmol), $Cu(OTf)_2$ (21.7 mg, 20 mol % based on **1**), $(NH_4)_2S_2O_8$ (68.5 mg, 0.3 mmol), and CH_3CN/H_2O = 500:1 (V/V, 3 mL) were added to a 35-mL reaction tube. Then the reaction mixture was stirred at 60 ºC for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100-200 mesh) using petroleum ether-EtOAc (6:1-3:1) as eluent to give pure product **3**.

***N*-acetyl-3-phenylquinoxaline-2-carboxamide (3aa):** Purified by column chromatography (petroleum ether/EtOAc, 6/1-3/1) as a white solid (76.0 mg, 87%). m.p. 116.5–168.7 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.26 (s, 1H), 8.23 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 8.19 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 7.96–7.93 (m, 1H), 7.91–7.87 (m, 1H), 7.68–7.66 (m, 2H), 7.54–7.53 (m, 3H), 2.55 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 172.2, 162.9, 154.4, 143.1, 142.0, 138.9, 138.3, 132.9, 131.1, 129.42, 129.37, 129.3, 128.9, 128.3, 25.3; IR (potassium bromide) (ν, cm^{-1}): 3234 (N-H), 1786 (C=O). HRMS (ESI) for $C_{17}H_{14}N_3O_2$ [M + H]$^+$: calcd: 292.1081, found: 292.1090.

Typical experimental procedure for the oxidative amidation of quinoxaline-2-carbaldehyde 1a with different nitriles 2

1a (0.3 mmol), $Cu(OTf)_2$ (21.7 mg, 20 mol % base on **1a**), and $(NH_4)_2S_2O_8$ (68.5 mg, 0.3 mmol, 1 equiv), and the **2**/H_2O mixture (500:1, V/V, 3 mL) were added to a 35-mL tube. Then the reaction mixture was stirred at 60 ºC for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100-200 mesh) using petroleum ether-EtOAc (6:1-3:1) as eluent to give pure **3ab**-**3ag**.

***N*-butyryl-3-phenylquinoxaline-2-carboxamide (3ab):** Purified by column chromatography (petroleum ether/EtOAc, 6/1-3/1) as a white solid (78.0 mg, 81%). m.p. 153.5–154.7 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.14 (s, 1H), 8.23 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 8.19 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.96–7.87 (m, 2H), 7.69–7.66 (m, 2H), 7.54–7.53 (m, 3H), 2.88 (t, J = 7.5 Hz, 2H), 1.77–1.69 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 174.9, 162.9, 154.2, 143.0, 142.4, 138.9, 138.3, 132.8, 131.1, 129.41, 129.38, 129.3, 128.9, 128.3, 39.3, 17.4, 13.6. IR (potassium bromide) (ν, cm^{-1}): 3235 (N-H), 1735 (C=O). HRMS (ESI) for $C_{19}H_{18}N_3O_2$ [M + H]$^+$: calcd: 320.1394, found: 320.1386.

***N*-isobutyryl-3-phenylquinoxaline-2-carboxamide (3ac):** Purified by column chromatography (petroleum ether/EtOAc, 6/1-3/1) as a white solid (48.9 mg, 51%). m.p. 209.8–210.1 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.91 (s, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.94-7.91 (m, 1H), 7.89-7.86 (m, 1H), 7.70-7.69 (m, 2H), 7.53-7.52 (m, 3H), 3.41-3.21 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.3, 163.4, 153.9, 143.4, 142.9, 139.1, 138.2, 132.5, 130.9, 129.46, 129.43, 129.36, 128.9, 128.4, 35.1, 18.6. IR (potassium bromide) (ν, cm^{-1}): 3229 (N-H), 1733 (C=O). HRMS (ESI) for $C_{19}H_{18}N_3O_2$ [M + H]$^+$: calcd: 320.1394, found: 320.1391.

Typical experimental procedure for the synthesis of *N*-acetyl-quinoline-2-carboxamides (7aa-ia), *N*-acetyl-phenanthridine-2-carboxamides (7ja-ma) and *N*-acetylbenzo[*d*]thiazole-2-carboxamide (8a)

6 (0.3 mmol), $Cu(OTf)_2$ (21.7 mg, 20 mol % based on **6**), $K_2S_2O_8$ (81.1 mg, 0.3 mmol, 1 equiv), and CH_3CN/H_2O = 500:1 were added to a 35-mL reaction tube. Then the reaction mixture was stirred at 90 ºC for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100-200 mesh) using petroleum ether-EtOAc (10:1-6:1) as eluent to give pure product **7**.

***N*-acetylquinoline-2-carboxamide (7aa):** Purified by column chromatography (petroleum ether/EtOAc, 10/1-6/1) as a white solid (52.3 mg, 81%). m.p. 139.2–140.8 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.82–7.78 (m, 1H), 7.68–7.65 (m, 1H), 2.66 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 172.1, 163.0, 147.6, 146.2, 138.0, 130.7, 129.9, 129.7, 128.9, 127.7, 118.6, 25.3. IR (potassium bromide) (ν, cm^{-1}): 3330 (N-H), 1710 (C=O). HRMS (ESI) for $C_{12}H_{11}N_2O_2$ [M + H]$^+$: calcd: 215.0815, found: 215.0820.

***N*-acetylbenzo[d]thiazole-2-carboxamide (8a):** Purified by column chromatography (petroleum ether/EtOAc, 10/1-6/1) as a yellow solid (29.5, 45%). m.p. 155.3–158.6 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.15–8.13 (m, 1H), 8.02–8.00 (m, 1H), 7.63–7.56 (m, 2H), 2.65 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 171.2, 161.4, 158.4, 152.4, 137.8, 127.8, 127.4, 125.1, 122.5, 25.4. IR (potassium bromide) (ν, cm^{-1}): 3348 (N-H), 1711 (C=O). HRMS (ESI) for $C_{10}H_9N_2O_2S$ [M + H]$^+$: calcd: 221.0379, found: 221.0383.

Mechanistic studies

Reaction of 1a in the Medium of CH_3CN-H_2O^{18}

1a (70.2 mg, 0.3 mmol), $Cu(OTf)_2$ (21.7 mg, 20 mol % based on **1a**), $(NH_4)_2S_2O_8$ (68.5 mg, 0.3 mmol, 1 equiv.), anhydrous CH_3CN (3 mL), and H_2O^{18} (5 equiv based on **1a**) were added to a 35-mL tube under N_2 atmosphere. Then the reaction mixture was stirred at 60 ºC for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100-200 mesh) using petroleum ether-EtOAc (6:1-3:1) as eluent to give pure product. The resulting product **3aa**/**3aa-O^{18}** sampled for LRMS analysis (see Figure *S1* in ESI).

Effect of Radical Scavenger TEMPO or BHT on the Model Reaction

Procedure (take TEMPO as an example): **1a** (70.2 mg, 0.3 mmol), $Cu(OTf)_2$ (21.7 mg, 20 mol % based on **1a**), $(NH_4)_2S_2O_8$ (68.5 mg, 0.3 mmol, 1 equiv), TEMPO (0.5 equiv; or 2 equiv), and the CH_3CN/H_2O mixture (500:1, V/V, 3 mL) were added to 35-mL tube. Then the reaction mixture was stirred at 60 ºC for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100-200 mesh) using petroleum ether-EtOAc (6:1-3:1) as eluent to give pure product. In the presence of 0.5 and 2.0 equiv of TEMPO, **3aa** was obtained in

53% and 0% yield, respectively. In the presence of 0.5 equiv of BHT, **3aa** was obtained in 64% yield. In the presence of 2.0 equiv of BHT, only trace amount of **3aa** was obtained.

Intermolecular Competition Experiment on 1a and 1a-*d*

1a-*d* was synthesized according to the reported procedure.[8b] **1a-*d*** was obtained in 96%-D enrichment. Analytical data for **1a-*d*/1a** (96/4): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.33 (s, 0.04H, **1a**), 8.33 (dd, J_1 = 8.4 Hz, J_2 = 1.0 Hz, 1H), 8.22 (dd, J_1 = 8.4 Hz, J_2 = 1.0 Hz, 1H), 7.97-7.86 (m, 2H), 7.74-7,67 (m, 2H), 7.59-7.55 (m, 3H). Procedure: A mixture of **1a** (33.7 mg, 0.144 mmol), **1a**-*d* (96%-D enrichment) (36.7 mg, 0.155 mmol), $Cu(OTf)_2$ (21.7 mg, 20 mol %), $(NH_4)_2S_2O_8$ (68.5 mg, 0.3 mmol), and CH_3CN/H_2O = 500:1 (V/V, 3 mL) were added to a 35-mL reaction tube. Then the reaction mixture was stirred at 60 ºC for 70 min. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100-200 mesh) using petroleum ether-EtOAc (10:1-6:1) as eluent to give pure recovered mixture of **1a** and **1a**-*d*. On the basis of ^{1}H NMR analysis, **1a** and **1a**-*d* were almost equally recovered. Therefore, the k_H/k_D was calculated to be 1.0 (Figure *S2* in ESI).

Quinoline-3-carbaldehyde 10, benzaldehyde 11, or butyraldehyde 12 reacted with 2a and water

8 (or 9, 10) (0.3 mmol), $Cu(OTf)_2$ (21.7 mg, 20 mol %), $K_2S_2O_8$ (81.1 mg, 0.3 mmol, 1 equiv), and CH_3CN/H_2O = 500:1 were added to a 35-mL reaction tube. Then the reaction mixture was stirred at 90 ºC for 6 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, samples were taken for GC-MS analysis. It was found that no desired products were detected while the starting materials were almost recovered.

Conflicts of interest

There are no conflicts to declare.

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