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Copper(II)-catalyzed oxidative [3 + 2] cycloaddition reactions of secondary amines with α -diazo compounds: facile and efficient synthesis of 1,2,3-triazoles Yi-Jin Li,^a Xue Li,^a Shao-Xiao Zhang,^b Yu-Long Zhao^{*a} and Qun Liu^a

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A novel copper-catalyzed [3 + 2] cycloaddition reaction of secondary amines with *a*-diazo compounds has been developed via a cross-dehydrogenative coupling process. The reaction involves a sequential aerobic oxidation/[3+2] 10 cycloaddition/oxidative aromatization procedure and provides an efficient method for the construction of 1,2,3triazoles in a single step in an atom-economic manner from readily available starting materials under very mild conditions.

- 15 The transition-metal-catalyzed cross-dehydrogenative coupling (CDC) reaction has been recognized as a powerful strategy to form new C-C and C-heteroatom bonds because it allows the use of simple nonfunctionalized substrates, thus making the synthetic routes shorter and more efficient.¹⁻⁴ Among these reactions, the CDC
- 20 reaction of α -C(sp³)-H centers of α -amino acid derivatives with various nucleophiles has been used as an efficient method to prepare α -substituted α -amino acid derivatives (Scheme 1, a).² On the basis of these reactions, taking the situ-generated α -aldimine A as an active intermediate, the transition-metal-catalyzed cross-dehydrogenative 25 coupling-cyclization aromatization reaction of N-arylglycine
- derivatives with alkynes or olefins was also carried out in the presence of oxidants (Scheme 1, b).³ Very recently, Xiao and coworkers reported a novel iridium-catalyzed [3 + 2] cycloaddition reaction of N-arylglycine derivatives with isocyanides under light ³⁰ irradiation condition (Scheme 1, c).⁴
- In addition, diazo compounds have attracted considerable interest because of their utility in various useful transformation.⁵ These compounds are ambiphilic reagents and electrophiles usually attack at the carbon atom of the diazo group, while the terminal nitrogen of the
- ³⁵ diazo group is attacked by nucleophiles.⁶ However, the harsh reaction of conditions. employment transition metals and oxidants in CDC reactions dramatically limited the application of diazo compounds as nucleophiles due to their facile decomposition under these conditions. In fact, the typical reaction between tertiary
- 40 amines and diazo compounds in the presence of transition metals is the direct C-H insertion involving metal carbenoid intermediates (Scheme 2, a).⁷ Recently, the first visible-light induced crossdehydrogenative coupling reaction between tertiary amines and diazo compounds was developed by Zhu and co-workers (Scheme 2, b).⁸ In
- $_{45}$ this context, the [3 + 2] cycloaddition reaction of secondary amines with α -diazo compounds via a CDC process is highly desired. As part of our continuing research on the carbon-carbon and carbonheteroatom bonds-formation reactions,9,12a herein we report the first copper-catalyzed [3 + 2] cycloaddition reaction of secondary amines
- 50 with α-diazo compounds via a CDC process, which works with a

broad range of α -amino acid derivatives, particularly N-alkylglycine derivatives (Scheme 2, c). Moreover, the reaction takes place unde very mild conditions with molecular oxygen as a co-oxidant and provides a new and efficient method for the construction of 1,2,3 55 triazoles in a single step in an atom-economic manner.









Initially, the reaction of glycine-derived amine 1a with ethyl diazoacetate (EDA) 2a was examined carefully to optimize the reaction conditions (Table 1). It was found that the [3+2 cycloaddition reaction of 1a (0.2 mmol) with 2a (1.0 mmol) coulu 65 afford the desired 1,2,3-triazole 3a in 84% yield in the presence c CuBr₂ (30 mol%) and DBU (0.6 mmol; DBU = 1.8diazabicyclo[5.4.0]undec-7-ene) in DMF (1.5 mL) at ror n temperature for 10 h under oxygen atmosphere (entry 1 Decreasing the amount of $CuBr_2$ and the ratio of 1a/2a led to low. 70 yields (entries 1, 2, 5 and 6). In addition, the desired 1,2,3-triazole 3/ was also achieved in 73% yield using air instead of pure oxyger

(entry 4). However, no reaction was observed under otherwisidentical conditions but in the absence of CuBr₂ (entry 7). Other catalysts, such as Cu(OTf)₂, CuBr, Cu(OAc)₂, CuI, FeCl₃ and AgOA 75 were less (Table 1, entries 8-11) or not effective (entries 12 and 13)

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Among the solvents tested, DMF seemed to be the best choice. Other solvents, such as CH₃CN, dichloroethane (DCE) and toluene, gave lower product yields (entries 14-16).

Table 1 Optimization of reaction conditions^a



Entr	y [M]	[0]	Ratio	Solvent	T/h	Yield ^b	
-	(mol%)	(1 atm)	(1a/2a)			(%)	
1	CuBr ₂ (10)	O_2	1/5	DMF	10	55	
2	$CuBr_{2}(20)$	O_2	1/5	DMF	10	74	
3	CuBr ₂ (30)	O_2	1/5	DMF	10	84^c	
4	$CuBr_{2}(30)$	air	1/5	DMF	12	73	
5	CuBr ₂ (30)	O_2	1/4	DMF	12	70	
6	$CuBr_{2}(30)$	O_2	1/3	DMF	12	59	
7		O_2	1/5	DMF	12	0	
8	$Cu(OTf)_2(30)$	O_2	1/5	DMF	10	60	
9	CuBr (30)	O_2	1/5	DMF	12	43	
10	$Cu(OAc)_2(30)$	O_2	1/5	DMF	10	67	
11	CuI (30)	O_2	1/5	DMF	12	63	
12	FeCl ₃ (30)	O_2	1/5	DMF	12	0	
13	AgOAc(30)	O_2	1/5	DMF	12	0	
14	$CuBr_{2}(30)$	O_2	1/5	CH ₃ CN	10	36	
15	$CuBr_2(30)$	O_2	1/5	DCE	10	41	
16	$CuBr_2(30)$	O_2	1/5	toluene	10	40	
^a Reaction conditions: 1a (0.2 mmol), 2a (0.6-1.0 mmol), [M] (0.02-							
0.06 mmol), DBU (0.6 mmol), solvent (1.5 mL), at room temperature							

for 10-12 h. ^b Estimated by ¹H NMR spectroscopy using dimethyl phthalate as an internal standard. ^c Isolated yield. Under the optimal reaction conditions (Table 1, entry 3), the scope and generality of the copper catalyzed [3 + 2] cycloaddition reaction

and generality of the copper-catalyzed [3 + 2] cycloaddition reaction of secondary amines **1** with ethyl diazoacetate **2a** was studied and the results are summarized in Table 2. It is obvious that the cycloaddition reaction showed broad tolerance for various R substituents of **1**. All selected substrates **1a-k**, bearing phenyl (entry 6), electron-rich (entries 1-5), electron-deficient (entry 7) aryl, heteroaryl (entry 8), 2naphthyl (entry 9), 1-naphthyl (entry 10) and alkyl R groups (entry

15 11) on the nitrogen atom, reacted with ethyl diazoacetate 2a to give the corresponding 1,2,3-triazoles 3a-k in moderate to high yields. In contrast, substrate 1g with electron-deficient aromatic R group and 1e with sterically hindered ortho-substituted aromatic R group required longer reaction times and gave comparatively lower product yields.
20 Similarly, the desired 1,2,3-triazoles 31 and 3m could also be obtained in 20% and 06% yields from substrates 11 and 1m bearing a

obtained in 80% and 96% yields from substrates **11** and **1m** bearing a methylamino (entry 12) and dimethylamino (entry 13) R^1 group, respectively.

²⁵ **Table 2** CuBr₂-Catalyzed [3 + 2] cycloaddition reaction of secondary amines **1** with ethyl diazoacetate $2a^{a}$

$R^{-N} = \frac{1}{1} = \frac{1}{N^{2}} \frac{CuBr_{2} (30 \text{ mol}\%), O_{2} (1 \text{ atm})}{OBU (3.0 \text{ eq.}), DMF, rt} = \frac{1}{EtO} = \frac{1}{3} \frac{V^{-R}}{V^{-R}}$								
Entry	1	R	R^1	T/h	3	Yield ^b (%)		
1	1a	4-MeC ₆ H ₄	OEt	10	3a	84		
2	1b	4-MeOC ₆ H ₄	OEt	10	3b	88		
3	1c	3-MeOC ₆ H ₄	OEt	10	3c	88		
4	1d	3-MeC ₆ H ₄	OEt	10	3d	75		
5	1e	2-MeC ₆ H ₄	OEt	17	3e	48		
6	1f	C_6H_5	OEt	12	3f	75		
7	1g	$4-ClC_6H_4$	OEt	16	3g	50°		
8	1ĥ	3-Thienyl	OEt	10	3h	72		

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9	1i	2-Naphthyl	OEt	10	3i	75^d		
10	1j	1-Naphthyl	OEt	16	3j	60^d		
11	1k	$C_6H_5(CH_2)_2$	OEt	10	3k	View4Article	Online	
12	11	4-MeC ₆ H ₄	NHMe	8 D	001: 31 0.10	39/C SO CO2	092A	
13	1m	4-MeC ₆ H ₄	NMe ₂	5	3m	96		
^a Reaction conditions: 1 (0.2 mmol), 2a (1.0 mmol), CuBr ₂ (0.06 mmol)								

DBU (0.6 mmol), DMF (1.5 mL) at room temperature under oxygen atmosphere for 5-17 h. ^{*b*} Isolated yield. ^{*c*} The reaction was performed at 80 $^{\circ}$ C.

The tandem process mentioned above not only carries out a coppercatalyzed [3 + 2] cycloaddition reaction of secondary amines with ethyl diazoacetate with molecular oxygen as a green co-oxidant for the first time, but also provides a simple and efficient route to 1,2,3triazoles from readily available starting materials in one-pot in an atom-economic manner. To test the generality of the new approach, the [3 + 2] cycloaddition reaction of selected secondary amines **1** with a series of α -diazocarbonyl compounds, such as 2-diazo-1phenylethanone **2b**, 2-diazo-1-(4-methoxyphenyl)ethanone **2c**, 2diazo-1-*p*-tolylethanone **2d**, 1-(4-chlorophenyl)-2-diazoethanone **2e** and 2-diazo-1-(thiophen-2-yl)ethanone **2f**, was investigated. As

1,2,3-triazoles **3n-v** can also be prepared in moderate to exceller yields (Scheme 3).



Scheme 3 CuBr₂-catalyzed [3 + 2] cycloaddition reaction of secondary ⁴⁵ amines **1** with α -diazo compounds **2b-f**.

To further probe the mechanisms for formation 3, some control experiments were designed and investigated. As a result, it was found that the yield of product 3a decreased greatly from 84 to 30% under the standard condition when BHT (2.0 equiv.; BHT = 2,6-di-tert-50 butyl-4-methylphenol) was used as a radical inhibitor (Scheme 4, a). This result implies that a radical process was involved in the overall CDC. In addition, according to the results of this transformation, we predicted that the glycine imine 4a may be a key intermediate in the reaction. Therefore, the reaction of glycine imine 4a with ethyl 55 diazoacetate 2a was further investigated. As expected, under otherwise identical conditions as above, the [3 + 2] cycloaddition reaction of glycine imine 4a with ethyl diazoacetate 2a could proceed, affording the desired product 3a in 55% yield (Scheme 4, b). I addition, the reaction of 4a with 2a under a nitrogen atmospher. 60 produced only a trace amount of **3a** (Scheme 4, c), indicating that molecular oxygen is crucial for the reaction. No desired product 3a was observed under otherwise identical conditions but in the absence of CuBr₂ (Scheme 4, d), which demonstrates that copper salt is also crucial for the above [3 + 2] cycloaddition reaction.

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Scheme 4. Control experiments for mechanistic studies.

On the basis of the above experimental results together with related reports,^{11,12} a possible mechanism of [3 + 2] cycloaddition reaction is ⁵ proposed in Scheme 5. Initially, the glycine-derived amines **1** are oxidized by CuBr₂ through a single-electron transfer (SET) process to generate the ammoniumyl radical cation intermediate **I** (Scheme 5).¹¹ Subsequently, hydrogen transfer or a combination of electron and proton transfer forms the iminium salt intermediate **II** (Scheme 5).¹¹ Finally, the reactive intermediate **II** undergoes a 1,3-dipolar cycloaddition reaction with α -diazo compounds **2** to afford the intermediate **III**, which then is oxidized by copper ion to produce the corresponding 1,2,3-triazole product **3** (Scheme 5).¹²



15 Scheme 5. Proposed mechanism for formation of 3.

In conclusion, we have developed a novel copper-catalyzed [3 + 2] cycloaddition reaction of secondary amines with α -diazo compounds for the first time via a CDC process. The reaction involves a ²⁰ sequential aerobic oxidation/[3+2] cycloaddition/oxidative aromatization procedure and provides a new and efficient method for the construction of 1,2,3-triazoles in a single step in an atom-economic manner. The reaction features readily available starting materials, simple operation, mild reaction conditions, good to ²⁵ excellent yields, broad substrate scope and using molecular oxygen as a green co-oxidant. Further studies are in progress.

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Notes and references

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