JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 30 May 2017

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Copper-Catalyzed Cross-Dehydrogenative N^2-Coupling of *NH*-1,2,3-Triazoles with *N,N* -Dialkylamides: *N*-Amidoalkylation of *NH*-1,2,3-Triazoles

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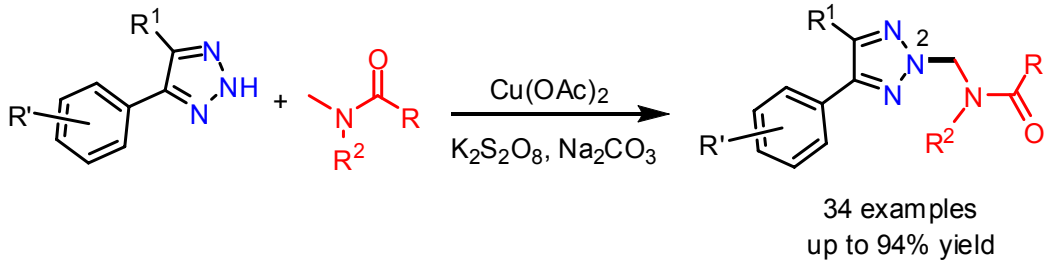


ABSTRACT: An efficient copper-catalyzed C-N bond formation by N-H/C-H cross-dehydrogenative coupling (CDC) between *NH*-1,2,3-triazoles and *N,N*-dialkylamides has been developed. The method provided *N*-amidoalkylated 1,2,3-triazoles with moderate to high yields, and the reactions showed high N^2-selectivities when 4,5-disubstituted *NH*-1,2,3-triazoles served as substrates.

INTRODUCTION

Cross-dehydrogenative coupling (CDC) reactions have emerged as powerful tools for organic synthesis because of their high atom- and step-economical characteristics,[1] which have also been widely applied in the functionalization of heterocyclic compounds in recent years.[2]

N-alkylamines and alkylamides, are good reaction partners for the CDC reactions. For example, DMF (*N,N*-dimethylformamide), which is widely recognized as a common solvent, can also be employed as a cheap, readily available reaction partner in CDC reactions.[3] Moreover, the CDC reaction of DMF is a straightforward method to introduce an amide group into a molecule. Indeed, some heterocyclic molecules with amide group have been found to show a range of interesting biological activities.[4]

1,2,3-triazoles have become important building blocks in organic chemistry in the past few years. They have received considerable attention and shown many applications in medicinal chemistry,[5] material chemistry,[6] synthetic organic chemistry[7] and other fields[8]. Most 1,2,3-triazoles are obtained by reactions of organic azides with other partners, such as click reactions of organic azides with alkynes[9], multicomponent reactions of organic azides with activated carbonyl compounds[10], and condensation reactions of organic azides with activated alkenes[11]. More recently, new azide-free strategies have also been developed.[12] These methods usually produce the N^1 or $N^{1'}$-substituted 1,2,3-triazoles, but are not suitable for producing N^2-substituted 1,2,3-triazole. N^2-substituted 1,2,3-triazoles were obtained mostly via post-*N*-functionalization of *NH*-1,2,3-triazoles with different reaction partners, including alkyl halides, alcohols, alkynes and alkenes.[13] Still, advances for the synthesis of diverse N^2-substituted 1,2,3-triazole were desirable.

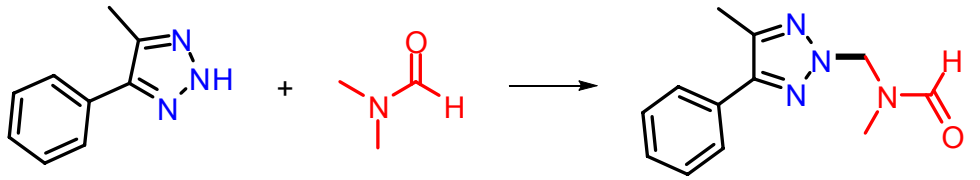
In continuation of our research for synthesis of new 1,2,3-triazole related heterocyclic compounds,[14] herein, we report a copper-catalyzed N-H/C-H cross-dehydrogenative coupling of *NH*-1,2,3-triazoles with different amides. By tuning the substituents, the

reactions gave N^2-coupling products with high yield.

RESULTS AND DISCUSSION

4-Methyl-5-phenyl-*2H*-1,2,3-triazole (**1a**) and DMF (*N,N*-dimethylformamide) were chosen as model substrates for the initial condition screening, the results are shown in Table 1. We proposed that methyl and phenyl groups could block the N^1 and $N^{1'}$ coupling sites, which might lead to high N^2-coupling selectivity.

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

entry	catalyst	oxidant	additive	conversion[b]	yield (%)[c]
1	CuCl	air	none	0	0
2	$CuCl_2$	air	none	0	0
3	CuCl	TBHP	none	60	54
4	CuBr	TBHP	none	69	61
5	$CuCl_2$	TBHP	none	65	59
6	$CuBr_2$	TBHP	none	75	68
7	CuO	TBHP	none	64	59
8	$Cu(NO_3)_2$	TBHP	none	48	43
9	$CuSO_4$	TBHP	none	55	51
10	$Cu(OAc)_2$	TBHP	none	85	76
11	$FeCl_2$	TBHP	none	30	23
12	$FeCl_3$	TBHP	none	35	32
13	$Cu(OAc)_2$	TBHP	Na_2CO_3	100	88
14	$Cu(OAc)_2$	TBHP	K_2CO_3	93	82
15	$Cu(OAc)_2$	TBHP	NaOAc	78	69
16	$Cu(OAc)_2$	TBHP	DBU	85	75
17	$Cu(OAc)_2$	DTBP	Na_2CO_3	<5	trace
18	$Cu(OAc)_2$	H_2O_2	Na_2CO_3	<5	trace

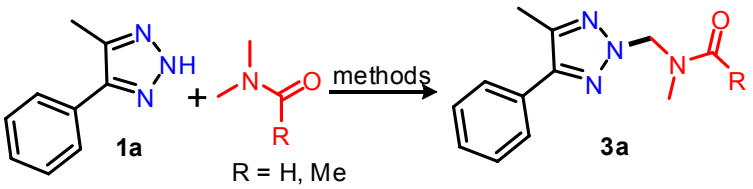
19	$Cu(OAc)_2$	$K_2S_2O_8$	Na_2CO_3	100	92
20	$Cu(OAc)_2$	BPO	Na_2CO_3	<5	trace
21	$Cu(OAc)_2$	DDQ	Na_2CO_3	<5	trace
22[d]	$Cu(OAc)_2$	$K_2S_2O_8$	Na_2CO_3	60	53
23	-	$K_2S_2O_8$	Na_2CO_3	100	90

[a]Reaction conditions: **1a** (0.3 mmol, 47.7 mg), **2a** (3mL as solvent), and oxidant (0.6 mmol, 2.0 equivalent, 162.2 mg), Na_2CO_3 (0.33 mmol, 1.1 equivalent, 35.0 mg), catalyst (0.06 mmol, 0.2 equivalent, 12.0 mg), 110 °C, 8 h; [b]Based on **1a**; [c]Isolated yields; [d] 80 °C.

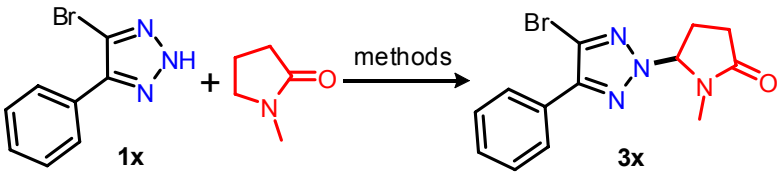
First, the reaction was performed in the presence of **1a** (0.3 mmol), CuCl (0.06 mmol, 0.2 equiv) in 3 mL DMF as solvent with air as the oxidant at 110 °C. After 5 hours there was no reaction at all. When CuCl was changed to $CuCl_2$, it gave the same result (Table 1, entries 1 and 2). However, when TBHP (*tert*-butyl hydroperoxide), a common oxidant, was used instead of air, after 5 hours we found that the desired **3a** was formed in 54% yield (entry 3). Inspired by this, other common copper salts were examined, which showed that $Cu(OAc)_2$ gave the best result (entries 4-10). Furthermore, other inexpensive iron salts were tested, including $FeCl_2$, $FeCl_3$ (entries 11 and 12), however, their catalytic efficiency was inferior to $Cu(OAc)_2$. Therefore, $Cu(OAc)_2$ was chosen as the catalyst for all further reactions. Interestingly, it was found that the addition of a base could promote the reaction, and Na_2CO_3 gave a better result (entries 13-16). In addition, other different oxidants were also investigated, including DTBP (di-*tert*-butyl peroxide), H_2O_2, BPO (benzoyl peroxide) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (entries 17-21), they failed to promote the reaction; however, when $K_2S_2O_8$ was chosen as the oxidant, the yield of **3a** rose to 92%, which also revealed high N^2 selectivity.[15] In addition, a relatively lower conversion and yield

was detected with a reaction temperature of 80 °C (entry 22). If the reaction run without copper catalyst (entry 23),[16] a satisfactory result was also obtained, the isolated yield of **3a** was up to 90%. In order to establish the best reaction condition, comparisons for different methods have also been made (Scheme 1). When DMF was served as reactant, the yield of the TBHP/TBAI protocol was only 36%, much lower than Cu or Cu-free protocols. When DMA or NMP was served as substrate for the coupling reaction under copper-free reaction condition, the yields were inferior to Cu-catalyzed reactions, while TBHP/TBAI was used instead of Cu or Cu-free reaction conditions, the yields of **3a** and **3x** were up to 76% and 88%, which were similar as the Cu-catalyzed protocol. However, the colors of the Cu-free reaction system or TBHP/TBAI protocol were darker than Cu-catalyzed reaction system generally. We suspected that the polymerization of the imine cation intermediates was easier under copper-free conditions. Thus, $Cu(OAc)_2/K_2S_2O_8/Na_2CO_3$ at 110 °C was chosen as the optimal reaction condition.

Scheme 1. Comparisons of the Reaction Conditions



method 1: 92% (R = H); 80% (R = Me);
method 2: 90% (R = H); 60% (R = Me);
method 3: 36% (R = H); 76% (R = Me).



method 1: 90%; method 2: 64%; method 3: 88%.

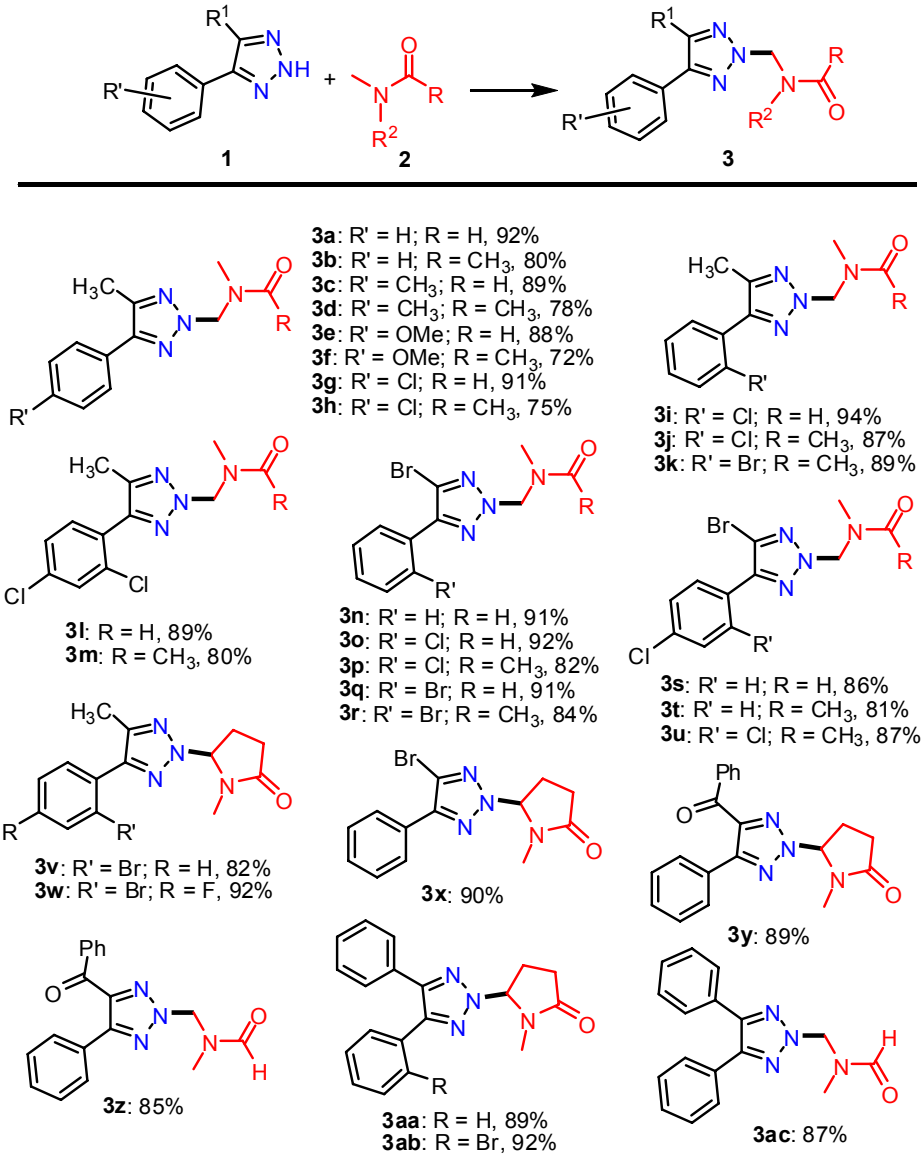
Reaction condition: **1a** and **1x** (200 mg, 1 equivalent), solvent (10 mL); isolated yields. method 1: $Cu(OAc)_2$ (0.2 equivalent), $K_2S_2O_8$ (2 equivalent), Na_2CO_3 (1.1 equivalent), 110°C; method 2: $K_2S_2O_8$ (2 equivalent), Na_2CO_3 (1.1 equivalent), 110°C; method 3: TBHP (3 equivalent), TBAI (0.1 equivalent), 110°C.

Then we set out to study the scope and limitation of this conversion with different *NH*-1,2,3-triazoles and amides (Scheme 2). In general, the reactions all performed well, the corresponding N^2-substituted products were less polar than other isomers. Firstly, 4-Me (or Br)-5-Ar-disubstituted *NH*-1,2,3-triazoles were checked due to the potentially high N^2 regioselectivities. In fact, the Me group and Br atom could indeed block the N^1 reaction sites. In all cases, the N^2-substituted product was formed predominantly. The structures of **3q** was identified by X-ray single crystal analysis.[17]

Then, other 4,5-disubstituted *NH*-1,2,3-triazoles, such as 4,5-diaryl 1,2,3-triazoles (**3aa**-**3ac**) and 4-benzoyl-5-phenyl-1,2,3-triazole(**3y**, **3z**), were suitable for this reaction and showed high N^2 regioselectivities. At the same time, both electron-donating functional groups, such as methoxy or methyl substituents, and electron-withdrawing groups, such as halogenated moieties in the aryl ring, were compatible with this transformation. The yield of N^2-coupling product was up to 94%. However, when the *1H*-1,2,3-triazole and

4-ethyl-5-methyl-1,2,3-triazole were tested, the reactions gave complex mixtures and the products were hard to be identified.

Scheme 2. Substrate Scope for the Synthesis of N^2-Amidoalkylated 1,2,3-Triazoles[a]



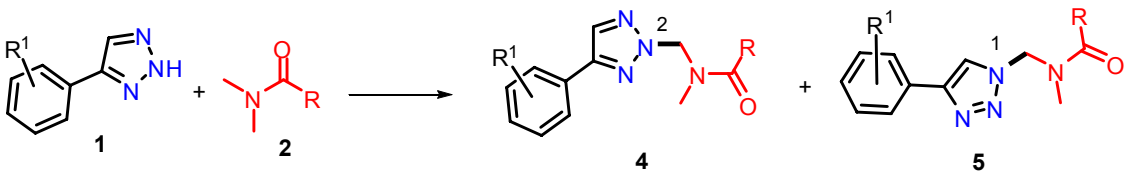
[a]Reaction conditions: **1** (0.3 mmol), **2** (3 mL as solvent), $Cu(OAc)_2$ (0.06 mmol), $K_2S_2O_8$ (0.6 mmol) and Na_2CO_3 (0.33 mmol), reaction temperature: 110 °C.

At the same time, commercially available amide solvents, such as DMF, DMA, were

suitable reaction partners to couple with *NH*-1,2,3-triazoles, although the reactions with DMA need more time to give the full conversion. However some side reactions or decomposition of the products could be happened over extended reaction time, which resulted in the loss of isolated yields. Furthermore, *N*-methyl-2-pyrrolidinone (NMP) was also a suitable substrate, which gave the N^2-coupling products with high yield. It should be pointed out that the reactions could be finished in 30 mins under standard reaction conditions. However, *N,N*-dimethylaniline piperidine-1-carbaldehyde *N,N*-diethylformamide and *N,N*-dimethylbenzamide cannot react in this reaction system.

To further investigate the reaction substrate scope, we tested 4-aryl substituted *NH*-1,2,3-triazoles (Table 2). The reactions also performed well. The corresponding N^2-coupling product was the major product generally. However, the regioselectivities were not very high, other N^1 products were also obtained.[18] The lower regioselectivities were similar to the results for the alkylation, arylation and alkenylation of 4-ary-1,2,3-triazoles.[13]

Table 2. 4-Aryl Substituted *NH*-1,2,3-Triazoles as Substrate[a]



entry	R^1	R	**4** yields[b] (%)	**5** yields[b] (%)
1	H-	H-	64 (**4a**)	18 (**5a**)

2	H-	CH_3-	50 (**4b**)	25 (**5b**)
3	4-CH_3-	CH_3-	59 (**4c**)	21 (**5c**)
4	4-OMe-	CH_3-	47 (**4d**)	27 (**5d**)
5	2-Br-	CH_3-	57 (**4e**)	20 (**5e**)

[a]Reaction conditions: **1** (0.3 mmol), **2** (3mL as solvent), $Cu(OAc)_2$ (0.06 mmol), $K_2S_2O_8$ (0.6 mmol) and Na_2CO_3 (0.33 mmol), 110 ^oC. [b]Isolated yields.

To identify the structures of *N*-amidoalkylated 1,2,3-triazoles, a gram-scale experiment[19] was done in order to obtain the N^1-coupling regioisomer (**3q'**) of **3q**. The structure was also confirmed by X-ray single crystal analysis.[17] Because the crystal structures of two regioisomers **3q** and **3q'** were obtained, it was beneficial to figure out the methods for the determination of the N^2 regioisomers for other reactions.

According to the ^{13}C NMR spectra of **3q** and **3q'**, there were significant differences between the CH_2 groups (which linked to 1,2,3-triazole) of the N^1(**3q'**) and N^2 (**3q**) isomers. The chemical shift of CH_2 group for N^2 isomer was 67.8 and 61.5 ppm (for two conformers), which located in lower field than N^1 isomer's (62.9 and 56.1 ppm, for two conformers). Also, the corresponding ^{13}C NMR spectra of two regioisomeric products for 4-aryl-substituted 1,2,3-triaoles gave the same information, such as **4e** and its N^1 isomer (**5e**). The chemical shift of CH_2 group for **4e** was located in 67.8 and 63.6 ppm. By contrast, the NMR spectra for **5e** showed one conformer, and the ^{13}C NMR chemical shift for CH_2 group was 60.1 ppm, which located in higher field. For other DMF or DMA coupling products, the corresponding N^2 isomers gave higher ^{13}C NMR chemical shifts for CH_2 group, which located in about 67 and 62 ppm (two conformers), such as **3d** and **3s**, while N^1

isomer gave lower chemical shifts. Moreover, some N^1 isomers only gave one conformer signal (Figure 1). Indeed, the N^1 and N^2 isomers of other triazoles and benzotriaoles showed the similar results.[13, 20] As for the coupling reactions with NMP, it was found that the reactions gave only N^2-coupling products because of a big steric hindrance.

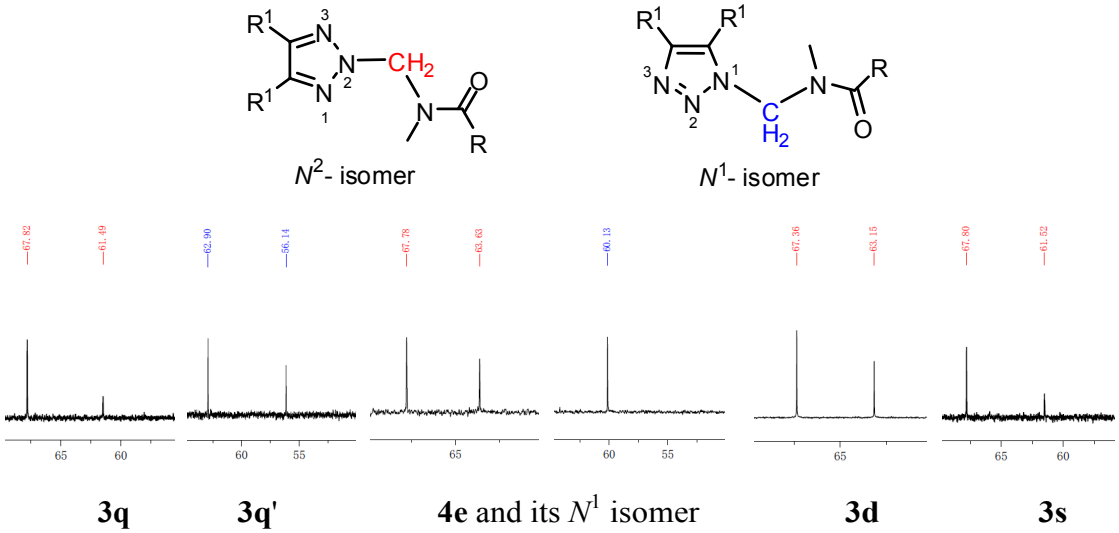
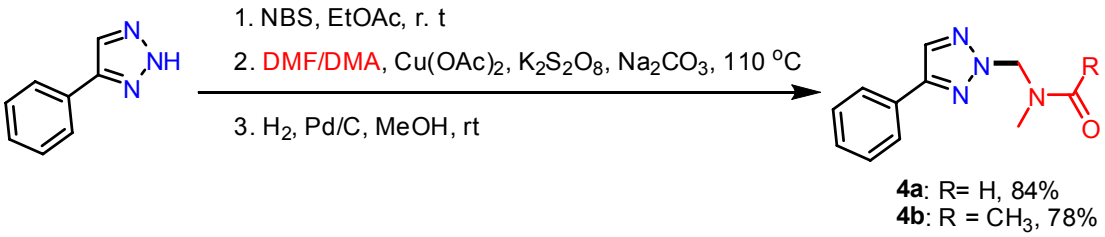


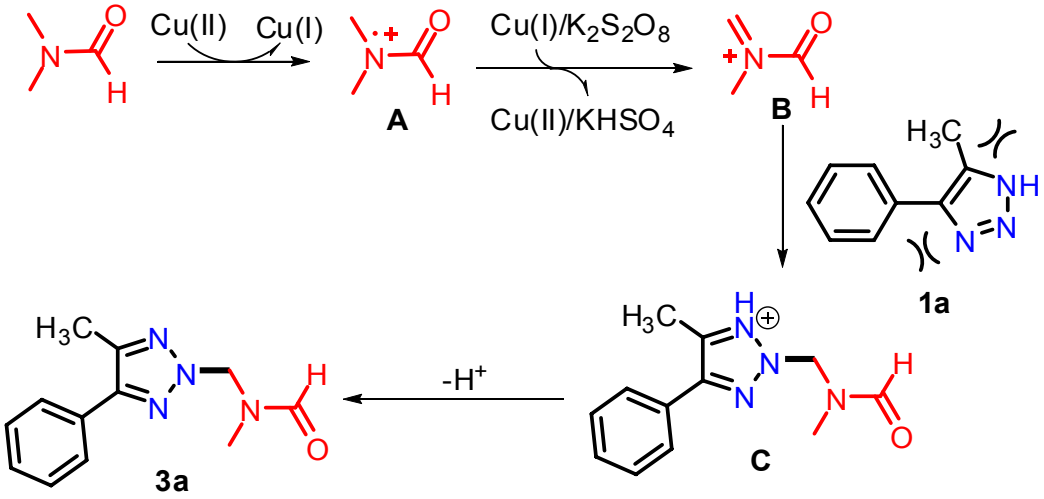
Figure 1. Analysis of ^{13}C NMR Spectra

In order to selectively synthesize 2,4-disubstituted 1,2,3-triazoles, a stepwise reaction strategy was developed. As shown in Scheme 2, the 4-phenyltriazole was first reacted with NBS (*N*-bromosuccinimide) to introduce a Br atom on the triazole ring[14b,21], then reacted with DMF or DMA. The corresponding N^2-amidoalkylated bromotriazoles were further reduced under catalytic hydrogenation condition (H_2, Pd/C) to give the 2-amidoalkylated 4-phenyl-1,2,3-triazoles in higher overall yields, which provide a highly selective synthesis of 2-amidoalkylated 4-aryl-1,2,3-triazoles (Scheme 3).



Scheme 3. An Alternative Synthesis of N^2-Amidoalkylated 4-Aryl-1,2,3-Triazoles

Based on experimental results and existing literature[2, 22], a postulated mechanism for this transformation has been put forward (Scheme 3). The initiation step is proposed to be a single electron transfer between Cu(II) and DMF to produce radical cation **A**. Next, the successive hydrogen atom abstraction from the radical cation A in the aid of Cu(I)/ $K_2S_2O_8$ forms the iminium ion **B**, which is selective attacked by N^2 site of triazole **1a** to form the intermediate **C**. Then lose a proton to form the product **3a**. The addition of a base is to neutralize the formed acid and further improve the reaction conversion (Scheme 4).



Scheme 4. A Plausible Mechanism for Oxidative N^2-Coupling

CONCLUSION

In conclusion, we report here a copper-catalyzed oxidative cross-dehydrogenative C-H/N-H

coupling reaction between *N*,*N*-dialkylamides and *NH*-1,2,3-triazoles. This method can give *N*-amidoalkylated 1,2,3-triazoles with high efficiency. By tuning the substituents on the *NH*-1,2,3-triazoles, the N^2-amidoalkylated 1,2,3-triazoles can be obtained in high selectivity and yield.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were determined on 400 and 600 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts are expressed in parts per million (δ), and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet), dd (double doublet), and coupling constants (*J*) were given in Hz. ^{13}C NMR spectra were recorded at 100 and 150 MHz in $CDCl_3$ solution. Chemical shifts as internal standard are referenced to $CDCl_3$ (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C NMR) as internal standard. High-resolution mass spectra (HRMS) were performed with Fourier-transform mass spectrometer by electrospray ionization and time of flight mass spectrometer by electrospray ionization. TLC was done on silica gel coated glass slides. All solvents were dried before use. 4-phenyltriazoles and 4-Methyl-5-phenyl-*2H*-1,2,3-triazoles were prepared according to literature procedure.[14a]

Typical Experimental Procedure: Synthesis of Br-substituted 1,2,3-triazole. To a solution of 4-phenyltriazole (500 mg, 3.45 mmol) in EtOAc (10 mL), was added NBS (920 mg, 5.18 mmol) at room temperature, the reaction was checked by TLC, After the completion of the reaction, the mixture was poured into water, and extracted by ethyl

acetate, washed with NaCl (aq), dried with anhydrous Na_2SO_4, then the solvent was removed under reduced pressure to obtain a yellow solid, and the crude product was purified by column chromatography [silica gel, PE-EtOAc (10:1 to 5:10)] to give (**1n**) a white solid (90%, 694mg).

Typical Experimental Procedure: Synthesis of *N*-amidoalkylated 1,2,3-triazoles. A 50 mL round-bottom flask equipped with a magnetic stir bar was charged with 4-methyl-5-phenyl-*2H*-1,2,3-triazole (47.7 mg, 0.3 mmol), DMF (3 mL as solvent), and $K_2S_2O_8$ (162.3 mg, 0.6 mmol), Na_2CO_3 (35 mg, 0.33 mmol), $Cu(OAc)_2$ (12 mg, 0.05 mmol). The mixture was then stirred at 110 °C in air for 0.5-6 h (TLC monitoring), then poured into H_2O (20 mL), adjusted the pH to neutral using 10% HCl, and extracted with EtOAc (3×20 mL). Next the organic phase was evaporated under vacuum, and the crude product was purified by column chromatography [silica gel, PE-EtOAc (10:1 to 2:1)] to give (**3a**) a white solid (89%, 61mg).

The procedure for the synthesis of 4a or 4b: To a solution of 4-phenyltriazole (200 mg, 1.38 mmol) in EtOAc (4 mL), was added NBS (367.8 mg, 2.07 mmol) at room temperature, the reaction was checked by TLC. The work-up procedure was the same as the synthesis of Br-substituted 1,2,3-triazoles, the obtained crude yellow solid can be used for the next step without further purification. The yellow solid reacted with DMF or DMA (4 mL) to obtain the N^2-amidoalkylated 4-bromo-triazoles (mentioned above as Typical Experimental Procedure: Synthesis of *N*-amidoalkylated 1,2,3-triazoles), then the N^2-amidoalkylated 4-bromo-triazoles and 10% Pd/C in methanol (8 mL) was stirred under atmospheric H_2 in a

50 mL schlenk bottle for 2 hours. Then triethylamine (3 mmol) was added to the mixture. After being stirred for 10 min, the mixture was filtered by diatomite. The filtrate was diluted with ethyl acetate (20 mL) and washed with water (20 mL). Then the organic phase was evaporated under vacuum, and the crude product was purified by column chromatography [silica gel, PE-EtOAc (10:1 to 2:1)] to give product **4a** (82%, 333mg) or **4b** (78%, 332mg).

4-bromo-5-phenyl-2H-1,2,3-triazole (**1n**) Whtie solid (90%, 694mg) m.p. 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.91 (s, 1H), 7.52–7.49 (m, 1H), 7.47 (d, J = 4.0 Hz, 1H), 7.46–7.42 (m, 1H), 3.52 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.2, 128.7, 127.4. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_8H_6BrN_3$: 223.9818, found 223.9817.

4-bromo-5-(2-chlorophenyl)-2H-1,2,3-triazole (**1o**) White solid (88%, 633mg) m.p. 81–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (m, 1H), 7.50–7.47 (m, 1H), 7.45–7.41 (m, 1H), 7.40–7.36 (m, 1H), 3.53 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 131.8, 130.9, 130.2, 127.1, 126.8, 123.2. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_8H_6BrClN_3$: 257.9428, found 257.9427.

4-bromo-5-(2-bromophenyl)-2H-1,2,3-triazole (**1q**) White solid (85%, 575mg) m.p. 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 1H), 7.46–7.31 (m, 3H), 3.53 (d, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 131.8, 131.0, 127.3, 123.5. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_8H_6Br_2N_3$: 301.89230, found 301.89246.

4-bromo-5-(4-chlorophenyl)-2H-1,2,3-triazole (**1s**) White solid (92%, 662mg) m.p. 192–193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 3.50 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.0, 128.7.

HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_8H_6BrClN_3$: 257.9428, found 257.9426.

4-bromo-5-(2,4-dichlorophenyl)-2H-1,2,3-triazole (**1u**) White solid (90%, 616mg) m.p. 148–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.38–7.36 (m, 1H), 3.51 (d, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 134.8, 132.9, 130.1, 127.3. ESI-MS(m/z): 290.9 $[M]^+$. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_8H_6BrCl_2N_3$: 291.9038, found 291.9034.

N-methyl-N-((4-methyl-5-phenyl-2H-1,2,3-triazol-2-yl)methyl)formamide (**3a**) White solid (92%, 132 mg) m.p. 60–62 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (s, 0.73H), 8.01 (s, 0.25H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 5.71 (s, 0.49H), 5.53 (s, 1.59H), 2.87 (s, 0.7H), 2.80 (s, 2.16H), 2.35 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8, 162.6, 146.0, 145.5, 142.2, 141.8, 130.4, 130.3, 128.4, 128.0, 127.8, 126.9, 66.4, 60.1, 33.3, 29.1, 11.5. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{15}N_4O$: 231.1240; found, 231.1235.

N-methyl-N-((4-methyl-5-phenyl-2H-1,2,3-triazol-2-yl)methyl)acetamide (**3b**) Light yellow oil (80%, 123 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (t, *J* = 7.8 Hz, 2H), 7.42 (q, *J* = 7.8 Hz, 2H), 7.36–7.33 (m, 1H), 5.87 (s, 0.87H), 5.71 (s, 1.25H), 3.08 (s, 1.23H), 3.03 (s, 1.82H), 2.46 (s, 3H), 2.43 (s, 1.85H), 2.13 (s, 1.24H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 145.8, 145.5, 142.0, 141.7, 130.8, 130.6, 128.5, 128.1, 127.9, 127.1, 67.3, 63.1, 35.1, 33.0, 21.7, 11.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{13}H_{17}N_4O$: 245.1397; found, 245.1398.

N-methyl-N-((4-methyl-5-(p-tolyl)-2H-1,2,3-triazol-2-yl)methyl)formamide (**3c**) Light

yellow solid (89%, 125mg) m.p. 66–68 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.4 Hz, 0.64H), 8.11 (d, *J* = 9.0 Hz, 0.22H), 7.61–7.45 (m, 2H), 7.28–7.15 (m, 2H), 5.80 (d, *J* = 9.0 Hz, 0.48H), 5.61 (d, *J* = 9.0 Hz, 1.53H), 2.99–2.95 (m, 0.7H), 2.92–2.87 (m, 2.12H), 2.45–2.39 (m, 3H), 2.38–2.30 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 162.7, 146.3, 145.8, 142.2, 141.8, 138.0, 129.2, 127.5, 126.9, 66.5, 60.2, 33.4, 29.3, 21.1, 11.6. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{13}H_{17}N_4O$: 245.1397; found, 245.1400.

N-methyl-N-((4-methyl-5-(p-tolyl)-2H-1,2,3-triazol-2-yl)methyl)acetamide (**3d**) Colorless oil (78%, 116 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61–7.52 (m, 2H), 7.25 (t, *J* = 8.4 Hz, 2H), 5.89 (s, 0.8H), 5.73 (s, 1.21H), 3.10 (s, 1.20H), 3.05 (s, 1.77H), 2.47 (s, 3H), 2.45 (s, 1.76H), 2.39 (d, *J* = 4.8 Hz, 3H), 2.16 (s, 1.14H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 171.3, 146.0, 145.7, 141.9, 141.7, 138.1, 137.9, 129.3, 128.1, 127.8, 127.1, 67.4, 63.2, 35.1, 33.2, 29.7, 21.8, 21.3, 11.8. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{14}H_{19}N_4O$: 259.1553; found, 259.1558.

N-((4-(4-methoxyphenyl)-5-methyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3e**) Light yellow oil (88%, 120 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 0.72H), 8.13 (s, 0.24H), 7.67–7.48 (m, 2H), 7.06–6.85 (m, 2H), 5.81 (s, 0.52H), 5.63 (s, 1.59H), 3.82 (d, *J* = 3.6 Hz, 3H), 2.99 (s, 0.69H), 2.92 (s, 2.10H), 2.44 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.0, 162.7, 159.5, 146.2, 145.7, 142.0, 141.7, 128.4, 123.0, 114.0, 66.6, 60.3, 55.2, 33.5, 29.4, 11.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{13}H_{17}N_4O_2$: 261.1346; found, 261.1340.

N-((4-(4-methoxyphenyl)-5-methyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**3f**)

Light yellow oil (72%, 104 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (t, *J* = 8.4 Hz, 2H), 6.96 (t, *J* = 7.8 Hz, 2H), 5.87 (s, 0.79H), 5.71 (s, 1.17H), 3.83 (d, *J* = 3.7 Hz, 3H), 3.09 (s, 1.11H), 3.04 (s, 1.61H), 2.44 (d, *J* = 3.0 Hz, 4.79H), 2.15 (s, 1.2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 159.6, 159.4, 145.8, 145. 5, 141.6, 141.4, 128. 5, 123.5, 123.2, 114.1, 67.3, 63.1, 55.3, 35.1, 33.1, 21.8, 11.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{14}H_{19}N_4O_2$: 275.1503; found, 275.1501.

N-((4-(4-chlorophenyl)-5-methyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3g**)

Light yellow solid (91%, 124mg) m.p. 74–76 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 0.73H), 8.14 (s, 0.23H), 7.60 (t, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 8.4 Hz, 2H), 5.82 (s, 0.5H), 5.65 (s, 1.5H), 3.01 (s, 0.77H), 2.91 (s, 2.23H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, CDCl3) δ 163.0, 162. 8, 145.3, 144.8, 142.4, 142.1, 134.2, 134.0, 129.2, 129.2, 129.0, 128.9, 128.8, 128.3, 66.8, 60.4, 33.6, 29. 5, 11.8. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{14}ClN_4O$: 265.0851; found, 265.0844.

N-((4-(4-chlorophenyl)-5-methyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**3h**)

Light yellow oil (75%, 108 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (t, *J* = 8.4 Hz, 2H), 7.43–7.36 (m, 2H), 5.87 (s, 0.93H), 5.73 (s, 1.22H), 3.11 (s, 1.27H), 3.04 (s, 1.7H), 2.46 (s, 3H), 2.44 (s, 1.67H), 2.15 (s, 1.32H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 144.9, 144.5, 142.0, 141.8, 134.2, 133.9, 129.4, 129.2, 128.8, 128.4, 67.5, 63.3, 35.3, 33.2, 21.8, 11.8. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{13}H_{16}ClN_4O$: 279.1007; found, 279.1012.

N-((4-(2-chlorophenyl)-5-methyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3i**)

Light yellow oil (94%, 129 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 0.70H), 8.12 (s,

0.23H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.35–7.25 (m, 3H), 5.83 (d, *J* = 1.2 Hz, 0.54H), 5.66 (d, *J* = 1.2 Hz, 1.59H), 2.97 (d, *J* = 1.2 Hz, 0.78H), 2.90 (d, *J* = 1.2 Hz, 2.22H), 2.22 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 162.7, 145.2, 144.7, 144.3, 143.9, 133.7, 131.6, 130.2, 130.0, 129.8, 129.7, 129.6, 129.3, 126.7, 126.6, 66.7, 60.4, 33.4, 29.4, 10.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{14}ClN_4O$: 265.0851; found, 265.0844.

N-((4-(2-chlorophenyl)-5-methyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**3j**)

Light yellow oil (87%, 125 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50–7.44 (m, 1H), 7.38–7.29(m, 3H), 5.91 (s, 0.87H), 5.76 (s, 1.21H), 3.09 (s, 1.2H), 3.05 (s, 1.68H), 2.43 (s, 1.73H), 2.26 (s, 3H), 2.16 (s, 1.26H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 144.8, 144.5, 144.0, 143.7, 133.8, 131.8, 131.7, 130.1, 130.1, 130.0, 129.9, 129.8, 129.6, 126.7, 67.5, 63.3, 35.1, 33.2, 21.8, 10.8. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{13}H_{16}ClN_4O$: 279.1007; found, 279.1004.

N-((4-(2-bromophenyl)-5-methyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**3k**)

White solid (89%, 121 mg) m.p. 122–124 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (m, 1H), 7.40–7.29 (m, 3H), 5.93 (s, 1H), 5.78 (s, 1.18H), 3.10 (s, 1.27H), 3.07 (s, 1.78H), 2.45 (s, 1.8H), 2.27 (s, 3H), 2.18 (s, 1.2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 146.34, 143.8, 133.1, 132.2, 131.5, 130.3, 127.3, 123.9, 67.8, 63.3, 35.0, 33.2, 21.8, 10.8. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{13}H_{16}BrN_4O$: 323.0502, found 323.0504.

N-((4-(2,4-dichlorophenyl)-5-methyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3l**)

Light yellow oil (89%, 116 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (s, 0.65H), 8.09 (s, 0.21H), 7.45–7.41(m, 1H), 7.27–7.20 (m, 2H), 5.79 (d, *J* = 1.2 Hz, 0.54H), 5.63 (d, *J* = 1.2

Hz, 1.54H), 2.95 (d, *J* = 1.2 Hz, 0.77H), 2.87 (d, *J* = 1.2 Hz, 2.18H), 2.18 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 162.7, 144.2, 143.9, 143.7, 135.4, 135.3, 134.4, 132.4, 129.6, 128.2, 128.0, 127.0, 66.8, 60.5, 33.5, 29.4, 10.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{13}Cl_2N_4O$: 299.0461; found, 299.0465.

N-((4-(2,4-dichlorophenyl)-5-methyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**3m**) Light yellow oil (80%, 110 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 9.0 Hz, 1H), 7.35–7.27 (m, 2H), 5.90 (s, 0.82H), 5.76 (s, 1.05H), 3.10 (s, 1.32H), 3.05 (s, 1.73H), 2.43 (s, 1.68H), 2.25 (s, 3H), 2.16 (s, 1.3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 143.9, 143.6, 135.5, 135.3, 134.6, 132.6, 132.5, 129.8, 128.6, 128.3, 127.1, 67.6, 63.4, 35.2, 33.2, 21.8, 10.8. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{13}H_{15}Cl_2N_4O$: 313.0617; found, 313.0624.

N-((4-bromo-5-phenyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3n**) Light yellow solid (91%, 118 mg) m.p. 68–70 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (s, 0.73H), 8.16 (s, 0.27H), 7.90 (d, *J* = 7.2 Hz, 2H), 7.48–7.40 (m, 3H), 5.87 (s, 0.61H), 5.70 (s, 1.66H), 3.05 (s, 0.86H), 2.95 (s, 2.25H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 146.8, 146.3, 129.2, 129.0, 128.7, 128.6, 128.5, 128.3, 127.3, 121.4, 121.0, 67.6, 61.3, 33.7, 29.6. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{11}H_{12}BrN_4O$: 295.0189; found, 295.0186.

N-((4-bromo-5-(2-chlorophenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3o**) White semisolid (92%, 117 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 0.73H), 8.19 (s, 0.29H), 7.55–7.49 (m, 1H), 7.45–7.34 (m, 3H), 5.92 (s, 0.62H), 5.76 (s, 1.48H), 3.08 (s, 0.83H), 2.99 (s, 2.2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 146.5, 134.0, 131.8, 130.9,

130.1, 127.4, 126.7, 124.4, 124.0, 67.8, 61.5, 33.9, 29.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{11}H_{11}BrClN_4O$: 328.9799; found, 328.9800.

N-((4-bromo-5-(2-chlorophenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**3p**)

Colorless oil (82%, 109 mg). ^{1}H NMR (400 MHz, CDCl3) δ 7.54–7.49 (m, 1H), 7.46–7.32 (m, 3H), 5.96 (s, 1H), 5.83 (s, 1.07H), 3.16 (s, 1.52H), 3.08 (s, 1.62H), 2.44 (s, 1.62H), 2.19 (s, 1.49H).^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 171.2, 146.0, 145.7, 134.0, 131.9, 131.7, 130.8, 130.7, 130.1, 130.0, 127.9, 127.5, 126.7, 126.6, 123.9, 123.5, 68.5, 64.4, 35.4, 33.3, 21.7, 21.6. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{13}BrClN_4O$: 342.9956, found 342.9962.

N-((4-bromo-5-(2-bromophenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3q**)

White solid (91%, 112 mg) m.p. 78–80 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 0.75H), 8.19 (s, 0.28H), 7.71 (d, J = 7.2 Hz, 1H), 7.46–7.30 (m, 3H), 5.93 (s, 0.6H), 5.76 (s, 1.54H), 3.08 (s, 0.88H), 2.99 (s, 2.27H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 147.8, 133.2, 131.9, 131.1, 129.4, 127.3, 124.3, 123.7, 67.8, 29.6. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{11}H_{11}Br_2N_4O$: 372.9294, found 372.9290.

N-((4-bromo-5-(2-bromophenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**3r**)

Colorless oil (84%, 108 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.65 (m, 1H), 7.43–7.38 (m, 2H), 7.37–7.30 (m, 1H), 5.97 (s, 1H), 5.84 (s, 1.11H), 3.15 (s, 1.51H), 3.08 (s, 1.65H), 2.44 (s, 1.66H), 2.19 (s, 1.52H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 171.4, 147.3, 146.9, 133.2, 131.9, 130.9, 129.89, 129.6, 127.2, 123.9, 123.6, 123.4, 77.3, 68.5, 64.4, 35.4, 33.3, 29.5, 21.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{13}Br_2N_4O$: 386.9451, found

386.9449.

N-((4-bromo-5-(4-chlorophenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3s**) White solid (86%, 110 mg) m.p. 65–66 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 0.71H), 8.18 (s, 0.28H), 7.94–7.81 (m, 2H), 7.49–7.37 (m, 2H), 5.88 (s, 0.59H), 5.72 (s, 1.46H), 3.08 (s, 0.88H), 2.97 (s, 2.16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 145.9, 145.4, 135.3, 128.9, 128.6, 126.9, 121.5, 121.0, 67.8, 61.5, 33.8, 29.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{11}H_{11}BrClN_4O$: 328.9799; found, 328.9797.

N-((4-bromo-5-(4-chlorophenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**3t**) White solid (81%, 108 mg) m.p. 89–90 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.76 (m, 2H), 7.53–7.33 (m, 2H), 5.92 (s, 1H), 5.80 (s, 1H), 3.16 (s, 1.47H), 3.06 (s, 1.46H), 2.44 (s, 1.5H), 2.18 (s, 1.53H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 171.2, 145.5, 145.0, 135.3, 135.0, 128.7, 127.3, 127.0, 121.0, 120.6, 68.5, 64.5, 35.6, 33.3, 21.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{13}BrClN_4O$: 342.9956, found 342.9959.

N-((4-bromo-5-(2,4-dichlorophenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**3u**) Colorless oil (87%, 112 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 7.2, 1.6 Hz, 1H), 7.40–7.32 (m, 2H), 5.95 (s, 1H), 5.83 (s, 1H), 3.16 (s, 1.5H), 3.07 (s, 1.5H), 2.43 (s, 1.5H), 2.19 (s, 1.5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.2, 145.0, 144.7, 136.3, 136.1, 134.9, 132. 6, 130.0, 127.1, 126.5, 126.1, 123.9, 123.5, 68.6, 64.6, 35.5, 33.3, 21.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{12}BrCl_2N_4O$: 376.9566, found 376.9561.

5-(4-(2-bromophenyl)-5-methyl-2H-1,2,3-triazol-2-yl)-1 methylpyrrolidin-2-one (**3v**) Light yellow oil (82%, 115 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 7.8 Hz, 1H), 7.38 (q,

J = 7.2 Hz, 1H), 7.36–7.32 (m, 1H), 7.32–7.27 (m, 1H), 5.98 (m, 1H), 2.97–2.90 (m, 1H), 2.75 (s, 3H), 2.63–2.56 (m, 2H), 2.48 (m, 1H), 2.26 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 146.1, 143.6, 133.0, 131.7, 130.3, 127.2, 123.7, 76.8, 28.9, 27. 4, 24.9, 10.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{14}H_{16}BrN_4O$: 335.0502; found, 335.0501.

5-(4-(2-bromo-4-fluorophenyl)-5-methyl-2H-1,2,3-triazol-2-yl)-1-methylpyrrolidin-2-one (**3w**) Colorless oil (92%, 254 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.38 (m, 1H), 7.32–7.25 (m, 1H), 7.12–7.05 (m, 1H), 5.94 (dd, *J* = 7.2, 2.4 Hz, 1H), 2.97–2.83 (m, 1H), 2.71 (s, 3H), 2.62–2.52 (m, 2H), 2.51–2.41 (m, 1H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 163.7, 161.2, 145.3, 143.7, 132.7, 132.6, 127.93, 127.90, 124.2, 124.1, 120.5, 120.2, 114.7, 114.5, 78.5, 28.9, 27.5, 24.9, 10.7. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{14}H_{14}BrFN_4NaO$: 375.0227, found 375.0223.

5-(4-bromo-5-phenyl-2H-1,2,3-triazol-2-yl)-1-methylpyrrolidin-2-one (**3x**) White solid (90%, 258 mg) m.p. 116–118 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.51–7.38 (m, 3H), 5.99 (dd, *J* = 7.6, 1.6 Hz, 1H), 2.99–2.85 (m, 1H), 2.78 (s, 3H), 2.68–2.56 (m, 1H), 2.55–2.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 146.3, 129.2, 128.63, 128.57, 127.3, 120.9, 79.6, 28.7, 27.7, 25.1. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{13}H_{13}BrN_4NaO$: 343.0165, found 343.0158.

5-(4-benzoyl-5-phenyl-2H-1,2,3-triazol-2-yl)-1-methylpyrrolidin-2-one (**3y**) White solid (89%, 247 mg) m.p. 112–114 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–7.97 (m, 2H), 7.80 (dd, *J* = 6.4, 3.2 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.42–7.37 (m, 3H), 6.10 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.00–2.87 (m, 1H), 2.82 (s, 3H), 2.73–2.62 (m, 1H),

2.62–2.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 175.1, 150.2, 142.5, 136.9, 133.5, 130.3, 129.3, 129.1, 128.6, 128.4, 128.3, 79.6, 28.6, 27.8, 25.3. HRMS (ESI-FTMS) m/z [M + Na]$^+$ calcd. for $C_{20}H_{18}N_4NaO_2$: 369.1322, found 369.1328.

N-((4-benzoyl-5-phenyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3z**) White solid (85%, 218 mg) m.p. 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.18 (s, 1H), 7.58–7.52 (m, 4H), 7.39–7.33 (m, 6H), 5.94 (s, 1H), 5.75 (s, 2H), 3.07 (s, 1H), 3.01 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.7, 145.8, 145.3, 130.4, 130.2, 128.6, 128.5, 128.42, 128.40, 128.2, 128.1, 67.0, 60.7, 33.6, 29.6. HRMS (ESI-FTMS) m/z [M + Na]$^+$ calcd. for $C_{18}H_{16}N_4NaO_2$: 343.1166, found 343.1169.

5-(4,5-diphenyl-2H-1,2,3-triazol-2-yl)-1-methylpyrrolidin-2-one (**3aa**) Light yellow solid (89%, 256 mg) m.p. 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.52 (m, 4H), 7.40–7.35 (m, 6H), 6.06 (dd, J = 6.8, 2.8 Hz, 1H), 3.04–2.93 (m, 1H), 2.83 (s, 3H), 2.68–2.58 (m, 2H), 2.56–2.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 145.4, 130.5, 128.59, 128.55, 128.2, 78.9, 28.9, 27.7, 25.2. HRMS (ESI-FTMS) m/z [M + Na]$^+$ calcd. for $C_{19}H_{18}N_4NaO$: 341.1373, found 341.1379.

5-(4-(2-bromophenyl)-5-phenyl-2H-1,2,3-triazol-2-yl)-1-methylpyrrolidin-2-one (**3ab**) White solid (92%, 243 mg) m.p. 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 8.0, 0.8 Hz, 1H), 7.50–7.41 (m, 2H), 7.43–7.36 (m, 2H), 7.34–7.24 (m, 4H), 6.07 (t, J = 4.8 Hz, 1H), 3.05–2.92 (m, 1H), 2.81 (s, 3H), 2.72–2.60 (m, 2H), 2.56–2.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 146.0, 144.5, 133.2, 132.4, 131.8, 130.6, 130.1, 128.54, 128.47, 127.5, 126.8, 124.2, 79.0, 28.9, 27.6, 25.0. HRMS (ESI-FTMS) m/z [M + Na]$^+$ calcd. for

$C_{19}H_{17}BrN_4NaO$: 419.0478, found 419.0483.

N-((4,5-diphenyl-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3ac**) White solid (87%, 229 mg) m.p. 105–107 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.17 (s, 1H), 8.03 (dd, *J* = 16.5, 7.5 Hz, 2H), 7.79–7.76 (m, 2H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.50–7.43 (m, 2H), 7.43–7.34 (m, 3H), 5.96 (s, 1H), 5.79 (s, 1H), 3.07 (s, 1H), 2.99 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.6,187.5, 162.9, 162.8, 150.4, 150.1, 143.0, 142.6, 136.8, 136.7, 133.6, 133.5, 130.3,130.2, 129.3, 129.2, 129.1, 128.9, 128.6, 128.5, 128.4, 128.32, 128.27, 67.6, 61.3, 33.8, 29.6. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{17}H_{16}N_4NaO$: 315.1206, found 315.1208.

N-((4-bromo-5-(2-bromophenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylformamide (**3q'**) White solid (5%, 61 mg) m.p. 196–198 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (s, 0.38H), 7.80 (dd, *J* = 7.8, 1.2 Hz, 0.57H), 7.74 (dd, *J* = 7.8, 1.2 Hz, 0.37H), 7.55–7.42 (m, 2.54H), 7.29–7.26 (m, 1.16H), 5.77 (d, *J* = 13.8 Hz, 0.4H), 5.69 (d, *J* = 4.8 Hz, 0.42H), 5.67 (d, *J* = 5.4 Hz, 0.56H), 5.62 (d, *J* = 14.4 Hz, 0.59H), 2.98 (s, 1.20H), 2.79 (s, 1.77H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.8, 161.5, 135.6, 135.1, 133.7, 133.2, 132.8, 132.3, 132.0, 131.7, 128.4, 127.9, 126.0, 125.9, 124.4, 124.2, 122.7, 122.4, 62.9, 56.1, 33.4, 29.1. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{11}H_{11}Br_2N_4O$: 372.9294, found 372.9288.

N-methyl-N-((4-phenyl-2H-1,2,3-triazol-2-yl)methyl)formamide (**4a**) Light yellow solid (64%, 89 mg) m.p. 58–60 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 0.74H), 8.16 (s, 0.26H), 7.90 (d, *J* = 3.6 Hz, 1H), 7.79 (d, *J* = 1.2 Hz, 1H), 7.43 (q, *J* = 7.2 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 5.92 (s, 0.57H), 5.75 (s, 1.4H), 3.02 (s, 0.76H), 2.94 (s, 2.25H). ^{13}C NMR (150

MHz, $CDCl_3$) δ 162.9, 162.6, 159.8, 148.5, 131.5, 131.2, 127.0, 126.9, 122.0, 114.0, 66.7, 60.3, 54.9, 33.2, 29.1. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{11}H_{12}N_4NaO$: 239.0903; found, 239.0900.

N-methyl-N-((4-phenyl-2H-1,2,3-triazol-2-yl)methyl)acetamide (**4b**) Colorless oil (50%, 76 mg). ^1H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.79 (t, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.37 (s, 1H), 5.97 (s, 0.91H), 5.82 (s, 1.01H), 3.11 (s, 1.42H), 3.05 (s, 1.4H), 2.47 (s, 1.48H), 2.16 (s, 1.46H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 159.9, 159.8, 148.4, 148.0, 131.2, 127.2, 122.5, 122.3, 114.1, 67.5, 63.4, 55.1, 35.1, 33.0, 21.5. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{12}H_{14}N_4NaO$: 253.1060; found, 253.1056.

N-methyl-N-((4-(p-tolyl)-2H-1,2,3-triazol-2-yl)methyl)acetamide (**4c**) Light yellow solid (59%, 86 mg) m.p. 84–86 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.74–7.58 (m, 2H), 7.30–7.15 (m, 2H), 5.96 (s, 0.89H), 5.82 (s, 0.98H), 3.11 (s, 1.26H), 3.05 (s, 1.31H), 2.47 (s, 1.4H), 2.39 (d, *J* = 3.2 Hz, 3H), 2.17 (s, 1.32H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.0, 135.4, 133.7, 130.9, 130.1, 129.9, 127.6, 121.9, 67.1, 60.8, 33.6, 29.6. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{13}H_{16}N_4NaO$: 267.1216; found, 267.1212.

N-((4-(4-methoxyphenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**4d**) Light yellow solid (47%, 67 mg) m.p. 81–83 °C. ^1H NMR (600 MHz, CDCl3) δ 7.81 (s, 1H), 7.71 (t, *J* = 7.8 Hz, 2H), 6.95 (t, *J* = 7.8 Hz, 2H), 5.94 (s, 0.85H), 5.79 (s, 1.13H), 3.82 (d, J = 4.2 Hz, 3H), 3.10 (s, 1.29H), 3.04 (s, 1.6H), 2.45 (s, 1.59H), 2.15 (s, 1.26H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 162.6, 148.8, 138.5, 131.9, 129.3, 129.2, 126.6, 125.6, 66.8, 60.4, 33.3, 29.2, 21.0. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{13}H_{16}N_4NaO_2$: 283.1166;

found, 283.1161.

N-((4-(2-bromophenyl)-2H-1,2,3-triazol-2-yl)methyl)-N-methylacetamide (**4e**) Light yellow solid (57%, 78 mg) m.p. 92–94 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.78–7.64 (m, 2H), 7.40–7.36 (m, 1H), 7.28–7.20 (m, 7.4 Hz, 1H), 5.99 (s, 0.9H), 5.86 (s, 1H), 3.14 (s, 1.38H), 3.07 (s, 1.41H), 2.47 (s, 1.38H), 2.17 (s, 1.37H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 148.7, 148.3, 131.9, 128.8, 128.6, 126.0, 67.8, 63.6, 35.2, 33.2, 21.7. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{14}BrN_4O$: 309.0346; found, 309.0343.

Mixture of N^1 [*N-methyl-N-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)formamide*] and $N^{1'}$ [N-methyl-N-((5-phenyl-*1H*-1,2,3-triazol-1-yl)methyl)formamide] product (**5a**) (18%, 25 mg), ritio of $N^{1'}$: N^1 =1:3 (based on ^{1}H NMR).

N-methyl-N-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)acetamide (**5b**) Light yellow oil (25%, 38 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.71 (d, J = 7.2 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.8 Hz, 1H), 5.72 (s, 2H), 3.03 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 147.9, 130.1, 128.6, 128.0, 125.8, 125.5, 125.4, 120.4, 59.9, 35.6, 21.4. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{12}H_{14}N_4NaO$: 253.1060; found, 253.1058.

N-methyl-N-((4-(p-tolyl)-1H-1,2,3-triazol-1-yl)methyl)acetamide (**5c**) Light yellow oil (21%, 31 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.71 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 7.2 Hz, 2H), 5.84 (s, 2H), 3.16 (s, 3H), 2.36 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 148.3, 138.0, 129.5, 129.4, 127.4, 125.9, 125.8, 125.5, 120.1, 60.0, 35.7, 21.5, 21.2. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{13}H_{16}N_4NaO$: 267.1216; found,

267.1215.

N-((4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl)methyl)-N-methylacetamide (**5d**) Light yellow oil (27%, 38 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.83 (s, 2H), 3.83 (s, 3H), 3.16 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 159.6, 148.0, 127.2, 126.9, 122.9, 119.6, 114.2, 114.1, 60.0, 55.2, 35.7, 21.5. HRMS (ESI-FTMS) m/z $[M + Na]^+$ calcd. for $C_{13}H_{16}N_4NaO_2$: 283.1166; found, 283.1164.

N-((4-(2-bromophenyl)-1H-1,2,3-triazol-1-yl)methyl)-N-methylacetamide (**5e**) Light yellow oil (20%, 27 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.10–8.04 (m, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 0.6 Hz, 1H), 5.89 (s, 2H), 3.20 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 145.8, 133.5, 131.1, 130.5, 129.4, 127.5, 123.9, 121.3, 60.1, 35.8, 21.6. HRMS (ESI-FTMS) m/z $[M + H]^+$ calcd. for $C_{12}H_{14}BrN_4O$: 309.0346; found, 309.0343.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/ x0xx00000x. Scanned copies of ^{1}H and ^{13}C NMR spectra of the synthesized compounds (PDF) Crystallographic data for compound **3q** and **3q'** (CIF).

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ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21002076, and 21441007), Graduate Education Innovation Fund of Wuhan Institute of Technology (CX2016162, CX2016167). Li, Y. thanks the Project of Natural Science Foundation of Hunan Province (2016JJ4072), and the Scientific Research Fund of Hunan Provincial Education Department (16A165).

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15 From the crude ^{1}H NMR, N^{1} and $N^{1'}$-coupling products are less than 5% in all, which cannot be separated and identified.

16 During the revision of this manuscript, Singh and coworkers reported a metal-free cross-dehydrogenative coupling reaction between *NH*-azoles and α-C(sp^3)-H containing amides, where *N*-amidoalkylation of *NH*-1,2,3-triazoles has been carried out under TBAI/TBHP oxidative conditions: Aruri, H.; Singh, U.; Kumar, M.; Sharma, S.; Aithagani, S. K.; Gupta, V. K.; Mignani, S.; Vishwakarma, R. A.; Singh, P. P. *J. Org. Chem.* **2017**, *82*, 1000.

17 Further information can be found in the CIF files. These crystal structures were deposited in the Cambridge Crystallographic Data Centre and assigned as CCDC (No: 1510061 and 1510062).

18 The separations of N^1 products sometimes include some $N^{1'}$ impurities (*see supporting information*).

19 To a solution of 4-bromo-5-(2-bromophenyl)-*1H*-1,2,3-triazole (1 g, 3.3 mmol) in DMF (20 mL), was added $Cu(OAc)_2$ (132 mg, 0.66 mmol), $K_2S_2O_8$ (1.78 g, 6.6 mmol) and Na_2CO_3 (0.38 g, 3.6 mmol), the mixture was stirred at 110 ^oC for 12 h. the isomer **3q'** was separated by silica gel chromatography from the mixture products in 5% yield.

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