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Copper(II)-Catalyzed C–H Nitrogenation/Annulation Cascade of Ketene *N,S*-Acetals with Aryldiazonium Salts: A Direct Access to N^2-Substituted Triazole and Triazine Derivatives

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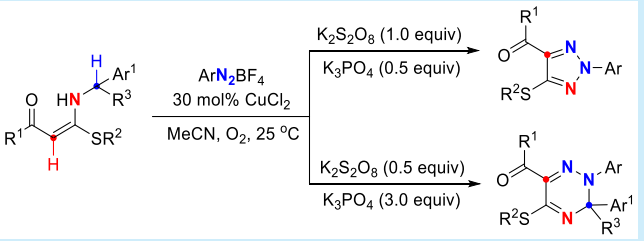
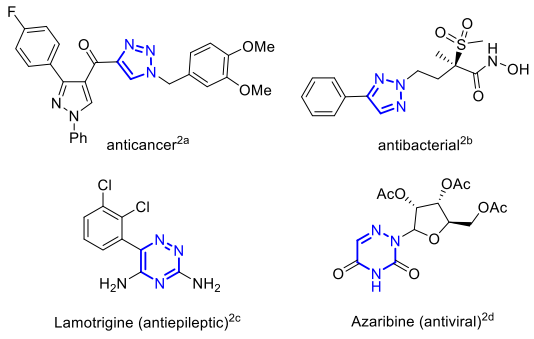
Supporting Information

ABSTRACT: Direct synthesis of N^2-substituted triazole and triazine derivatives has been a challenge in *N*-heterocyclic chemistry. Under copper(II) catalysis ketene *N,S*-acetals, that is, alkylthio-substituted enaminones, efficiently reacted with aryldiazonium salts to allow the regioselective generation of functionally diverse N^2-substituted 1,2,3-triazoles and 2,3-dihydro-1,2,4-triazines. The oxidant and base-dependent reaction yielded the five- and six-membered *N*-heterocyclic products, respectively. The synthetic protocol features broad substrate scopes and good functional group tolerance under mild conditions. The mechanistic studies have revealed that the reaction proceeds via alkenyl azo/imino hydrazone intermediates.



N-Heterocyclic compounds have been demonstrated to have versatile applications in pharmaceuticals, agrochemicals, functional materials, and coordination chemistry,[1] among which 1,2,3-triazole and 1,2,4-triazine derivatives have shown diverse anticancer, antibacterial, antiepileptic, and antiviral activities (Scheme 1).[2] Due to their potential applications, general methods for their regioselective synthesis have been strongly desired. In this regard, many efforts have been devoted to the synthesis of N^1-substituted 1,2,3-triazoles by means of Huisgen cycloaddition,[3] transition-metal-catalyzed azide–alkyne cycloaddition,[4] and other metal-free[5] or azide-free[6] strategies. However, N^2-substituted 1,2,3-triazoles can not be readily accessed, and their direct synthesis has remained a great challenge due to the uncontrollable regioselectivity of the conventional synthetic reactions. Thus, N–H functionalization of *N*H-1,2,3-triazoles has usually been used to make N^2-substituted 1,2,3-triazole derivatives, including N^2-arylation,[7] alkylation,[8] allylation,[9] and vinylation[10] (Scheme 2a). Oxidative cyclization of arylhydrazones[11] and azobenzenes,[12] copper(I)-catalyzed carboamination cascade between vinyl azides and aryldiazonium salts,[13] and coupling of oxime acetates with diazonium tetrafluoroborates[14] have also been applied for the same purpose. It should be noted that use of explosive azides is potentially dangerous,[13] while in the azide-free method only *p*-methoxybenzenediazonium tetrafluoroborate worked well as the coupling partner at a relatively high temperature.[14] Despite the significant advances, direct methods for the regioselective synthesis of N^2-substituted 1,2,3-triazoles, starting from azide-free substrates under mild conditions, is still highly desirable.

Scheme 1. Representative Biologically Active 1,2,3-Triazole and 1,2,4-Triazine Derivatives



The condensation reaction of 1,2-diketones and equivalents with hydrazines has been utilized to prepare 3,5-disubstituted or 3,5,6-trisubstituted 1,2,4-triazines (Scheme 2b).[15] The metal-free methods such as $BF_3{\cdot}OEt_2$-promoted ring-opening/cyclization/oxidation cascade of aziridines with *N*-tosylhydrazones[16] and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)-mediated [3 + 3] cyclization of imines with α-diazocarbonyls[17]

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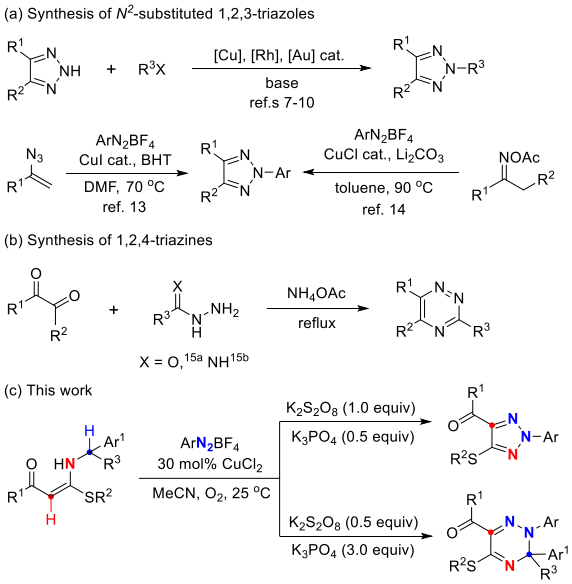
Scheme 2. Strategies for the Construction of 1,2,3-Triazole and 1,2,4-Triazine Derivatives



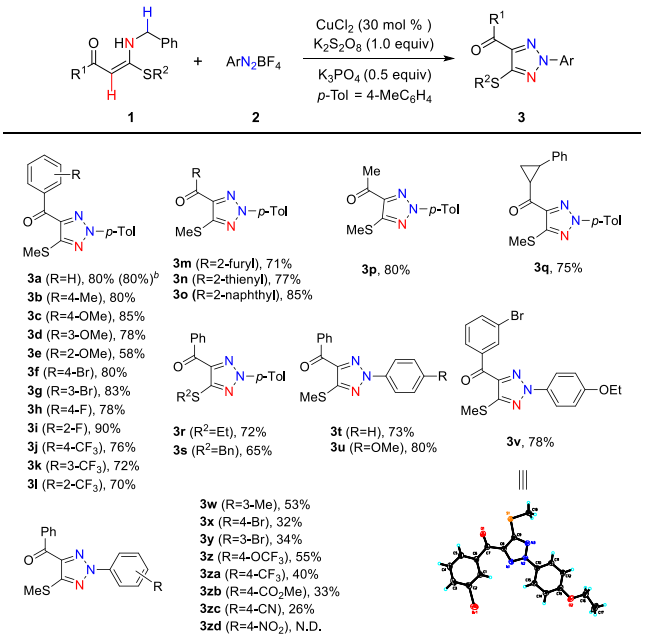
were also applied for the synthesis of 3,5,6-trisubstituted-1,2,4-triazines. However, these methods usually afford C-3-, C-5-, and/or C-6-substituted 1,2,4-triazines. Although copper-catalyzed tandem nucleophilic ring-opening/intramolecular oxidative amidation of *N*-tosylaziridines with hydrazones was successfully applied for the synthesis of N^1-substituted 1,2,4-triazines,[18] and polycyclic 1,2,4-triazine scaffolds were synthesized by [3 + 3] annulation,[19] the synthetic methods for N^2-substituted 1,2,4-triazines from readily accessible starting materials and with excellent functional group tolerance have been seldom reported.

Transition-metal-catalyzed tandem C−H functionalization/annulation strategy has been well explored for the construction of *N*-heterocycles through C−C/C−N bond formation.[20] However, such a strategy has not yet been successfully applied for the direct synthesis of triazole and triazine derivatives. Enaminones have been known for the synthesis of *N*-heterocyclic compounds.[21,22] Recently, we found that *α*-oxo ketene *N*,*S*-acetals, that is, alkylthio-substituted enaminones, could act as diverse building blocks for functionalized *N*-heterocycles.[22] Thus, we envisioned that C−H diazotization of these enaminones with aryldiazonium salts might be employed to synthesize five- and six-membered *N*-heterocyclic 1,2,3-triazole and 1,2,4-triazine derivatives. Herein, we disclose a Cu(II)-catalyzed annulation protocol of alkylthio-enaminones with aryldiazonium salts for the tunable direct synthesis of N^2-aryl-substituted 1,2,3-triazole and 2,3-dihydro-1,2,4-triazine derivatives under mild conditions (Scheme 2c).

Initially, the reaction of (*Z*)-3-(benzylamino)-3-(methylthio)-1-phenylprop-2-en-1-one (**1a**) and *p*-methylbenzenediazonium tetrafluoroborate (**2a**) was conducted to optimize the reaction conditions for the formation of N^2-aryl-substituted 1,2,3-triazole (**3a**) and 2,3-dihydro-1,2,4-triazine (**4a**). The reaction conditions for synthesis of **3a** were optimized to molar ratio of **1a**:**2a** = 1:2, 30 mol % $CuCl_2$ as the catalyst, 1.0 equiv of $K_2S_2O_8$ as the oxidation, 0.5 equiv of K_3PO_4 as base, MeCN as the solvent, 25 °C, 5 h in O_2. The reaction conditions for synthesis of **4a** were optimized to molar ratio of **1a**:**2a** = 1:2, 30 mol % $CuCl_2$ as the catalyst, 0.5 equiv of $K_2S_2O_8$ as the oxidation, 3.0 equiv of K_3PO_4 as base, MeCN as the solvent, 25 °C, 5 h in O_2 (see the Supporting Information for details). Compound **3a** was considered to be formed from the intermolecular oxidative olefinic C−H nitrogenation/debenzylation cascade of **1a** and **2a**, and compound **4a** was generated from the intermolecular oxidative double C−H nitrogenation/annulation process.

Next, the protocol generality for the synthesis of N^2-substituted 1,2,3-triazoles **3** was explored under the optimal conditions (Scheme 3). Thus, the benzylamine-derived ketene

Scheme 3. Synthesis of N^2-Aryl-Substituted 1,2,3-Triazoles 3[a]



[a]Conditions: **1** (0.30 mmol), **2** (0.60 mmol), $CuCl_2$ (0.09 mmol), $K_2S_2O_8$ (0.30 mmol), K_3PO_4 (0.15 mmol), MeCN (3 mL), 0.1 MPa O_2, 25 °C, 5 h. [b]Scale-up synthesis: **1a** (1 mmol), **2a** (2 mmol), $CuCl_2$ (0.3 mmol), $K_2S_2O_8$ (1.0 equiv), K_3PO_4 (0.5 equiv), MeCN (10 mL).

N,*S*-acetals were used to react with various aryldiazonium tetrafluoroborates to give N^2-aryl-1,2,3-triazole derivatives. In most of the cases using *p*-tolyldiazonium tetrafluoroborate (**2a**), the target products were obtained in good to excellent yields (70−90%) with a tolerance for methyl, methoxy, bromo, fluoro, and trifluoromethyl on the aryl group of the aroyl moieties in the *α*-aroyl ketene *N*,*S*-acetal substrates, and **3a** could also be obtained in 80% yield on a 1 mmol scale of **1a**. *o*-OMe and *o*-CF_3 groups exhibited a negative steric impact on the reaction efficiency, leading to **3e** (58%) and **3l** (70%), respectively, whereas *o*-F facilitated the reaction to form product **3i** (90%). Usually, the *m*-substituted *α*-aroyl ketene *N*,*S*-acetals produced the target products less efficiently than the corresponding *para*-substituted analogues. *α*-Heteroaroyl ketene *N*,*S*-acetals, that is, the furoyl- and thienoyl-based ketene *N*,*S*-acetals, were also suitable substrates for the reaction, affording **3m** and **3n** in 71−77% yields. The ketene *N*,*S*-acetals functionalized at the *α*-position by 2-naphthoyl, acetyl, and cyclopropylcarbonyl reacted well with **2a** to give the corresponding products **3o** (85%), **3p** (80%), and **3q** (75%), respectively. The ethylthio- and benzylthio-based *N*,*S*-acetals

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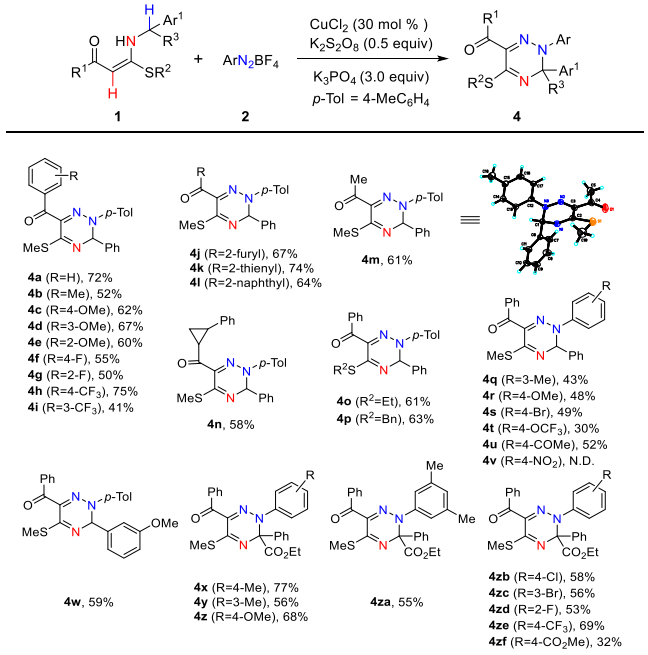
1r and **1s** exhibited a reactivity lower than that of their methylthio analogue **1a**, and their reactions with **2a** gave **3r** (72%) and **3s** (65%), respectively, while the reaction of **1a** with **2a** gave **3a** in 80% yield. When the aryl groups in ArN_2BF_4 salts were changed to phenyl, 4-methoxy, and 4-ethoxyphenyl, the target products **3t**–**3v** were yielded in 73–80% yields, whereas the relatively sterically hindered *m*-methyl, and electron-withdrawing 3-Br, 4-Br, 4-OCF_3, 4-CF_3, 4-CO_2Me, or 4-CN on the aryl moiety of the aryldiazonium salts diminished the yields from 55% to 26% for **3w**-**3zc**. Product **3zd** could not be detected when 4-NO_2-benzenediazonium tetrafluoroborate was used as the substrate. It should be noted that the aryldiazonium salts except for 4-OMe- and 4-OMe-2-Me-benzenediazonium tetrafluoroborates did not react under Jiang's conditions[14] (Scheme 2a). The molecular structure of compound **3v** was further confirmed by the X-ray single-crystal crystallographic determination (Scheme 3, see the Supporting Information for details).

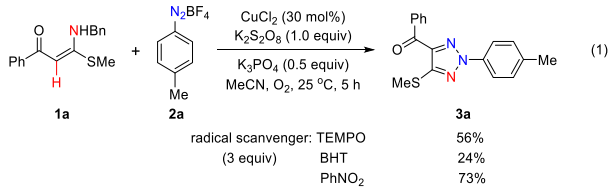
Then, the synthetic methodology was investigated for the synthesis of N^2-aryl-2,3-dihydro-1,2,4-triazine derivatives (**4**) (Scheme 4). Under the optimal conditions, benzylamine-derived ketene *N*,*S*-acetals efficiently reacted with *p*-tolyldiazonium tetrafluoroborate (**2a**) to give the target products **4a**–**4p** in 50–75% yields. During the reaction, compounds of type **3** were always accompanied as the side products, which led to less efficient isolation of products **4** than compounds **3** from the reaction mixtures. The substituent effect varied from the substituent groups on the aroyl moieties of the ketene *N*,*S*-acetal substrates. For example, the 4-CF_3-bearing ketene *N*,*S*-acetal reacted with **2a** to form the target product **4h** in 75% yield, while the 2-F- and 3-CF_3-substituted α-aroyl ketene *N*,*S*-acetals gave the products **4g** and **4i** in 50% and 41% yields, respectively, which is contrary to the phenomenon observed for the synthesis of N^2-aryl-1,2,3-triazoles **3i**–**3k** (72–90%) (Scheme 3). The α-furoyl- and thienoyl-based ketene *N*,*S*-acetals also efficiently reacted with **2a** to afford **4j** and **4k** (67–74%). 2-Naphthoyl-, acetyl-, and cyclopropylcarbonyl-functionalized ketene *N*,*S*-acetals reacted with **2a** less efficiently than those reactions employed for the synthesis of compounds **3o**–**3q** (75–85%) (Scheme 3), giving the corresponding products **4l** (64%), **4m** (61%), and **4n** (58%). The EtS- and BnS-based ketene *N*,*S*-acetals also reacted less efficiently with **2a** than the corresponding methylthio-*N*,*S*-acetals, forming **4o** (61%) and **4p** (63%). When the aryl groups in aryldiazonium salts were changed to 3-methyl- and 4-methoxyphenyls, the target products **4q** and **4r** were obtained in moderate yields (43–48%). Halogen (4-Br) and electron-withdrawing (4-OCF_3 and 4-COMe) substituents on the aryl moiety of the aryldiazonium salts also diminished the yields of **4s** (49%), **4t** (30%), and **4u** (52%), respectively, while 4-NO_2-benzenediazonium tetrafluoroborate did not react with **1a** under the same conditions. Other benzylamines such as *m*-MeO-benzylamine and ethyl 2-amino-2-phenylacetate were also utilized to prepare the ketene *N*,*S*-acetal substrates for the double C–H nitrogenation/annulation cascade. It was found that the *m*-MeO-benzylamine-derived ketene *N*,*S*-acetal exhibited a reactivity inferior to that of ketene *N*,*S*-acetal **1a** generated from the *N*H-unprotected benzylamine, and its reaction with **2a** formed **4w** in 59% yield, whereas the ketene *N*,*S*-acetal derived from the ethoxycarbonyl group-functionalized benzylamine showed a higher reactivity than **1a**, and its reaction with **2a** gave the corresponding product **4x** in 77% yield. In a similar fashion, such a relatively reactive ketene *N*,*S*-acetal was used to react with various aryldiazonium salts, affording compounds **4y**-**4zf** (32–69%). Diverse functional groups were tolerant, including methyl, methoxy, chloro, bromo, fluoro, trifluoromethyl, and methoxycarbonyl. The molecular structure of compound **4m** was unambiguously confirmed by the X-ray single-crystal crystallographic determination (Scheme 4, see the Supporting Information for details).

To gain insights into the reaction mechanism, the reaction of ketene *N*,*S*-acetal **1a** with aryldiazonium salt **2a** was conducted in the presence of 3.0 equiv of a radical scavenger such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-*di*-*tert*-butyl-4-methylphenol (BHT) or a single electron transfer (SET) inhibitor nitrobenzene under the optimal reaction conditions for the synthesis of compounds **3**, and the target product **3a** was formed in 24–73% yields (eq 1). These results exclude a radical reaction pathway. In our previous work,[23] alkenyl azobenzenes could be obtained from the interaction of α-oxo ketene dithioacetals and aryldiazonium salts, thus we reasonably envisioned that similar alkenyl azobenzenes might also be generated as the reaction intermediates in the current transformation.The control experiments were then conducted by carrying out the reaction of ketene *N*,*S*-acetal **1c** with *o*-fluorobenzene-diazonium tetrafluoroborate (**2m**) in the absence of oxidant $K_2S_2O_8$ under an argon atmosphere or performing it under the optimal conditions for synthesizing **3**

Scheme 4. Synthesis of N^2-Aryl-Substituted 2,3-Dihydro-1,2,4-triazines 4[a]



[a]Conditions: **1** (0.30 mmol), **2** (0.60 mmol), $CuCl_2$ (0.09 mmol), $K_2S_2O_8$ (0.15 mmol), K_3PO_4 (0.90 mmol), MeCN (3 mL), 0.1 MPa O_2, 25 °C, 5 h.



(1)

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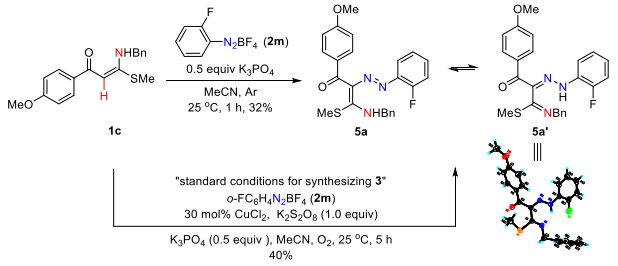
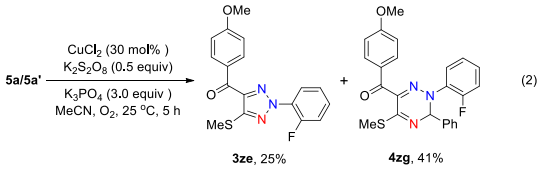
(Scheme 5). In both cases, the corresponding target products of types **3** and **4** were not isolated in a detectable amount from

Scheme 5. Control Experiments

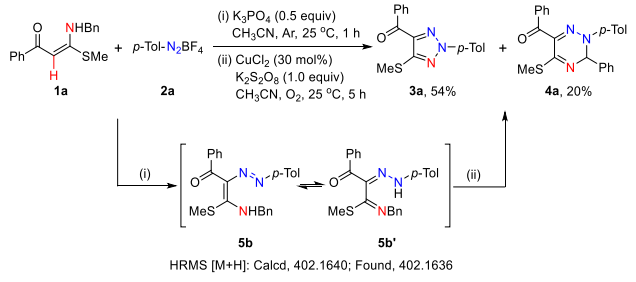


the reaction mixture. However, the azo-hydrazone tautomer **5a**/**5a′** was isolated in 40% yield (Scheme 5). Recrystallization of the tautomer gave single crystals of compound **5a′** suitable for structural characterization by the X-ray single-crystal crystallographic determination (Scheme 5, see the Supporting Information for details). It is noteworthy that the NMR spectra of compound **5a′** only revealed a mixture of **5a**/**5a′** in $CDCl_3$ due to the quick tautomerization between **5a′** and **5a** in solution.[24] The ^{15}N NMR spectrum of **5a**/**5a′** revealed six resonance signals at δ = −35.27, −35.66, −51.98, −65.21, −237.49, and −241.84 ppm by using nitromethane (δ = 0.0) as the external standard. This result suggests that **5a** and **5a′** exist as the discrete isomers in solution. To further identify the possibility of **5a**/**5a′** as the reaction intermediates, the **5a**/**5a′** tautomer was treated under the standard conditions for synthesizing compounds **4**. To our delight, 1,2,3-triazole **3ze** (25%) and 2,3-dihydro-1,2,4-triazine **4zg** (41%) were isolated from the reaction [eq 2], which suggests that **5a**/**5a′** may be



the reaction intermediates toward the N^2-arylated 1,2,3-triazole and 2,3-dihydro-1,2,4-triazine derivatives. A one-pot, two-step procedure was also investigated by initial treatment of **1a** with **2a** in the presence of 0.5 equiv K_3PO_4 under an argon atmosphere, followed by reacting with 1.0 equiv $K_2S_2O_8$ in the presence of the $CuCl_2$ catalyst under an oxygen atmosphere, giving **3a** (54%) and **4a** (20%) as the final products by ^1H NMR analysis (Scheme 6). Analysis of the reaction mixture from the first step action by HRMS method revealed a strong molecular ion peak (m/z = 402.1636; calcd for **5b** and **5b′**,

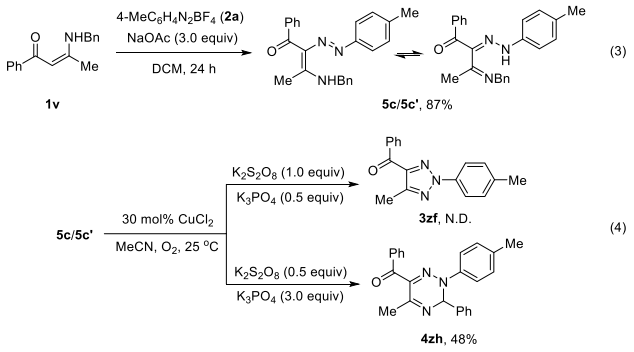
Scheme 6. One-Pot, Two-Step Procedure



HRMS [M+H]: Calcd, 402.1640; Found, 402.1636

402.1640) corresponding to species **5b**/**5b′**. This result further demonstrates that the alkenyl azo or imino hydrazone compounds may be the reaction intermediates.

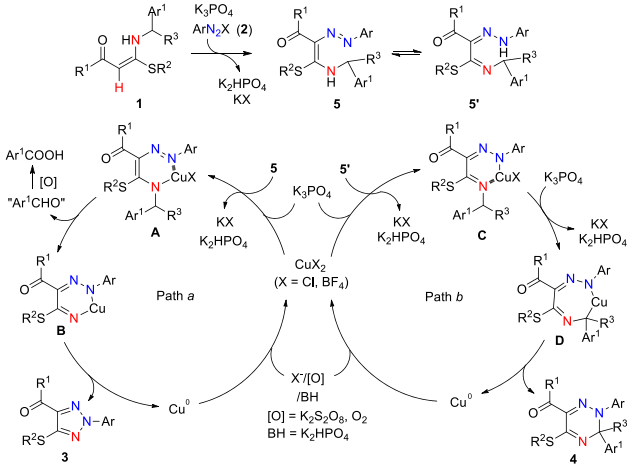
Moreover, enaminone **1v** with replacement of the methylthio functionality by a methyl, reacted with **2a** in the presence of NaOAc to unambiguously form azo-hydrazone tautomer **5c**/**5c′** in 87% yield [eq 3]. The **5c**/**5c′** tautomer was



then treated under the standard conditions for synthesizing compounds **3** or **4**, respectively. 1,2,3-Triazole **3zf** was not detected, but 2,3-dihydro-1,2,4-triazine **4zh** was obtained in 48% yield from the reaction (eq 4), further suggesting that the azo/hydrazone compounds may be the reaction intermediates.

A plausible reaction mechanism is proposed in Scheme 7. Initially, ketene *N*,S-acetal **1** undergoes alkenyl C−H

Scheme 7. Control Experiments



diazotization with aryldiazonium tetrafluoroborate **2** to generate alkenyl azo/imino hydrazone intermediate **5**/**5′** under the basic conditions.[23,24] Interaction of the copper(II) catalyst with **5** forms complex **A** from which debenzylation proceeds[25] to give the imino-Cu(II) hydrazone complex **B**. Analysis of the reaction mixture by HRMS revealed a molecular ion peak of benzoic acid (HRMS [M − H]: m/z = 121.0295; calcd for $PhCOO^-$, 121.0289). Reductive elimination from intermediate **B** affords the product of type **3** and copper(0) species. In the presence of the oxidant and base, the copper(II) catalyst is regenerated from Cu(0) (path a). The imino hydrazone intermediate **5′** interacts with the copper(II) catalyst to form imino-Cu(II) hydrazide complex **C**. A Cu(II)-promoted intramolecular benzylic C−H bond activation proceeds to yield the benzyl-Cu(II) hydrazone complex **D**. Reductive elimination from intermediate **D** gives

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the product of type **4** and regenerates the copper(II) catalyst under the oxidative conditions (path b). The formation of PhCOOH may be attributed to the in situ generated benzyl chloride (or dichloride) which is hydrolyzed to benzyl alcohol (or benzaldehyde) during the reaction. Both benzyl alcohol and benzaldehyde can be oxidized to PhCOOH under the oxidation conditions. It should be noted that benzyl chloride was not detected in the reaction mixture.

In conclusion, copper(II)-catalyzed regioselective synthesis of N^2-aryl-substituted 1,2,3-triazole and 2,3-dihydro-1,2,4-triazine derivatives was achieved by means of tunable C−H nitrogenation/annulation cascades of ketene *N*,*S*-acetals and aryldiazonium salts under mild conditions. The protocol features simple operation, readily available starting materials, broad substrate scope, and good functional group tolerance. The target products were obtained in good to excellent yields, avoiding use of explosive azides. The mechanism studies have implicated that the reaction proceeds through alkenyl azo/imino hydrazone intermediates. The present method provides a direct protocol to access N^2-aryl-substituted 1,2,3-triazole and 2,3-dihydro-1,2,4-triazine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04335.

Experimental materials and procedures, NMR of compounds, and X-ray crystallographic analysis for compounds **3v**, **4m**, and **5a′** (PDF)

Accession Codes

CCDC 1830695, 1830698, and 1863889 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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