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Copper(I)-Mediated Carboamination of Vinyl Azides by Aryldiazonium Salts: Synthesis of N^2-substituted 1,2,3-Triazoles

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A copper(I)-mediated carboamination cascade reaction between vinyl azides and aryldiazonium salts is described. Functionally diverse N^2-substituted 1,2,3-triazoles were obtained in moderate to good through novel difunctionalization of vinyl azides by aryldiazonium salt sources. This method has a wide scope, good functional-group tolerance and insensitivity to ambient atmosphere.

1,2,3-triazoles[1] have been ubiquitous in pharmacological developments, chemical biology applications, and materials science because of their privileged chemical structure and properties as five-membered heterocycles. Recently, 1,2,3-triazoles have also received significant interest as chelates,[2] auxiliaries for C-H activation[3] and efficient carbene precursors.[4] Traditionally, the synthesis of triazoles has been affected by the classical Huisgen 1,3-dipolar cycloaddition reaction,[5] which suffers from slow kinetics and poor regioselectivity. The metal-catalyzed azide-alkyne cycloaddition[1,6], especially method using Cu(I) catalysis[6a,b] overcame the deficiencies of this reaction for preparing 1,4- and 1,5-substituted 1,2,3-triazoles. However, concise and regioselective strategies[7] for the synthesis of N^2-substituted 1,2,3-triazoles are still rare, with most methods requiring postmodification.[8,9a,9b] This has seriously hindered the widespread application of these molecules, which have been used as critical components in orexin receptor antagonist MK-4305,[9a-b] SYK kinase inhibitors,[9c] and ALK5 inhibitors.[9d]

Vinyl azides, particular electron-rich alkenes, were first prepared one hundred years ago.[10] These active synthons have undoubtedly emerged as especial azides and enamine analogues for series of nitrogen-containing molecules such as N-vinyl-1,2,3-triazoles, pyrroles, pyridines, etc., albeit as a “sleeper” for a long period because of their high inherent reactivity.[1b,11] Among the multitude of transformations, one classical pathway by generating iminyl species has drawn considerable attention because of its versatile assembly of critical chemical bonds (Figure 1 a). However, the reaction modes have been limited to capturing monofunctional groups, such as carbon, nitrogen or sulfur sources,[11] rather than the successful and flexible 1,1-difunctionalization of aliphatic olefins.[12] Additionally, aryldiazonium salts have been successfully applied as aryl or aryldiazenyl precursors for more than one century.[13] However, aryldiazonium salts acting as both aryl and aryldiazenyl reagents in reported protocols are still rare.[14] These underdevelopments have severely restricted the widespread utilization of vinyl azides and aryldiazonium salts in organic synthesis. Hence, the development of a dual-functionalization at the β-carbon of a vinyl azide using an arenediazonium salts is urgently needed.

Because of our sustained interest in readily available vinyl azides,[1c,15] we envisioned that dual-functionalization at the β-carbon of vinyl azides with aryldiazonium salts could be achieved for the preparation of 1,2,3-triazoles. The initial experimental results confirmed this hypothesis and showed an intramolecular carboamination and ring-closure reaction between vinyl azide and the aryldiazonium salt through a dual-functionalization process at the β-carbon of the vinyl azide with a sole aryldiazonium salt source (Figure 1 b). Here, we describe this new copper(I)-mediated, powerful and general method for synthesizing diverse N^2-substituted 1,2,3-triazoles with moderate to high yields.

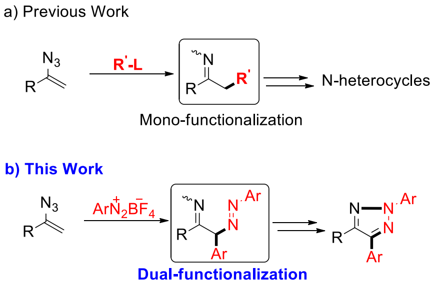

Figure 1 Functionalizations of vinyl azides.

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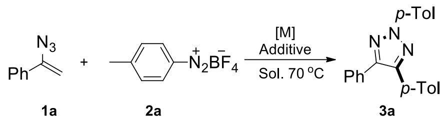
Table 1 Optimization of the reaction conditions.[a]



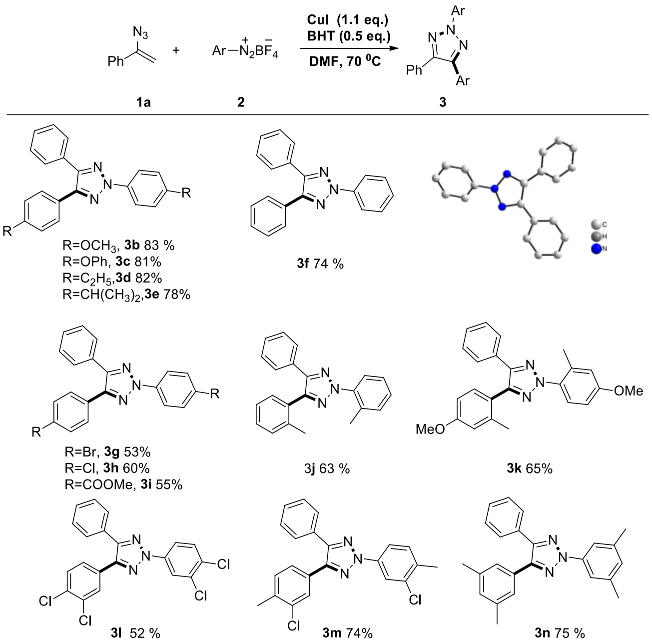
Entry	[M]	Sol.	Additive	Yield[b]/%
1	CuI	DMSO	---	15[c]
2	---	DMSO	---	0
3	CuI	DMSO	---	<5[c,d]
4	CuI	DMSO	---	56
5	CuBr	DMSO	---	43
6	$CuCl_2$	DMSO	---	25
7	$NiCl_2$	DMSO	---	0
8	CuI	DMF	---	65
9	CuI	DCE	---	0
10	CuI	Toluene	---	0
11	CuI	DMF	K_2CO_3	26
12	CuI	DMF	HOAc	47
13	CuI	DMF	AIBN	77
14	CuI	DMF	TEMPO	70
15	CuI	DMF	BHT	83

Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol.), [M] (0.55 eq.), additive (0.5 eq.), solvent (1 mL), 70 °C, 6 h. [b]Isolated yield. [c]0.01 mmol CuI was used. [d]Reaction temperature is 25 °C. DMSO = dimethyl sulfoxide, DMF = dimethylformamide, DCE = 1,2-dichloroethane, AIBN=2,2'-azobis(2-methylpro- pionitrile), TEMPO=2,2,6,6-tetramethylpiperidinooxy and BHT=2,6-di-tert-butyl-4-methylphenol.

To determine the optimized conditions, the reaction with model substrates α-azido styrene (**1a**) and 4-methylphenyldiazonium tetrafluoroborate (**2a**) was initially carried out in DMSO at 70 °C. Encouragingly, the product **3a** was obtained with a 15% yield (Table 1, entry 1). Notably, the success of the desired transformation strongly depended on the metal catalyst and the reaction temperature (entries 2 and 3). With the aim of increasing the yield of product **3a**, we further increased the amount of copper(I) catalyst, which led to the formation of the product in a moderate yield (entry 4). Compared to other metal salts, CuI afforded the highest yield of **3a** (entries 4-7). The solvent also dramatically influenced the reaction. DMF gave **3a** in best yield (entries 8-10). Additional additives were also tested, including K_2CO_3, HOAc, AIBN, TEMPO and BHT (entries 11-15), with BHT being the most efficacious in enhancing reactivity.

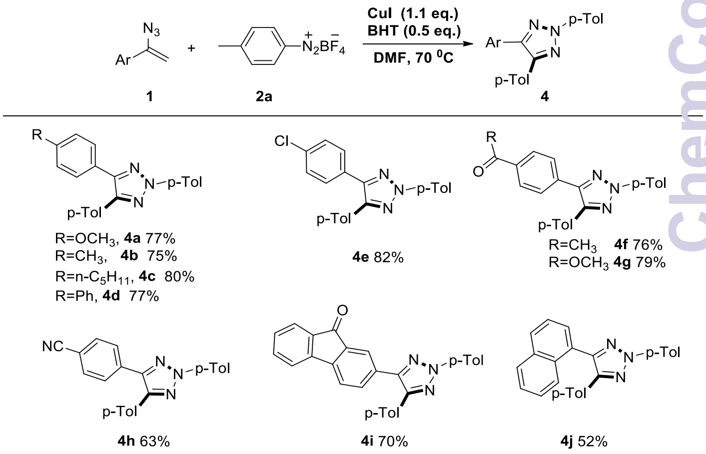
Having optimized conditions, we turned our attention to investigating the scope of substitution patterns (Schemes 1 and 2). We first explored the substrate scope by varying the aryldiazonium salts (**2b**-**2n**) (Scheme 1). Aryl rings with electron-donating substituents (OMe, OPh, C_2H_5 and $CH(CH_3)_2$) afforded the corresponding products (**3b**-**3e**) in good yields. The structure of **3f** was further confirmed by single-crystal X-ray analysis (see the Supporting Information).[16] The reactions also proceeded well with electron-deficient aryldiazonium salts (Cl, Br, COOMe), affording the products (**3g**-**3i**) under the optimized conditions. These groups were left intact under the reaction conditions for further synthetic diversification. Those substrates with ortho-methyl substituent at the aryl ring (**2j**-**2k**) were smoothly converted to yield 1,2,3-triazole units (**3j**-**3k**) with slight difference yields. Other poly-substituted electron-deficient or electron-rich triazole products (**3l**-**3n**) were also delivered in good yields.

Scheme 1 Scope of aryldiazonium salts tolerated. [a]



[a]Reaction conditions: 1a (0.5 mmol), 2 (1.5 mmol), CuI (0.55 mmol), BHT (0.25 mmol), DMF (1 mL), 70 °C, 6-10 h.

Scheme 2 Scope of vinyl azides. [a]



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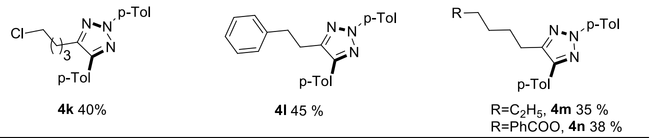
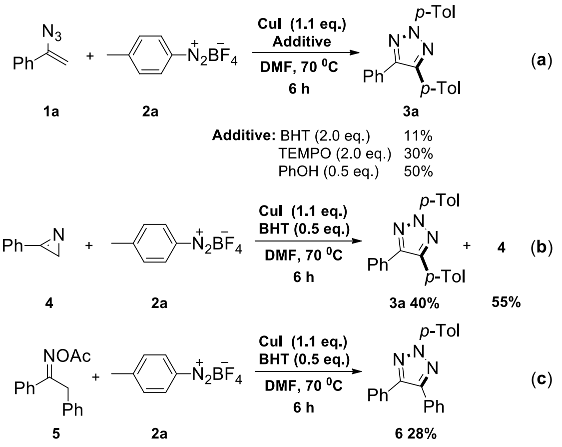


[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), CuI (0.55 mmol), BHT (0.25 mmol), DMF (1 mL), 70 °C, 6-10 h. [b]1 mmol Na_2CO_3 was used instead of BHT.

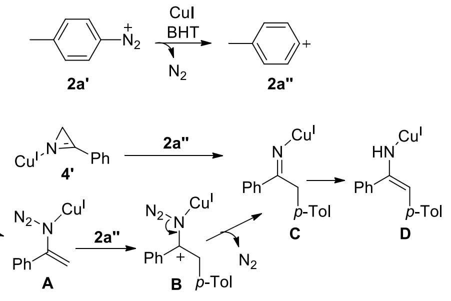
Encouraged by these results, we subsequently evaluated general applicability of diverse vinyl azides (**1a**-**1n**) with aryldiazonium salts **2a**. Overall, as shown in Scheme 2, vinyl azides with various substituents on the benzene ring smoothly participated in the difunctionalization and cyclization reaction, delivering the corresponding products (**4a**-**4n**) in moderate to good yields. Vinyl azides bearing electron-donating or -poor substituents on the arene ring (**1a**-**1h**) afforded the homologous products(**4a**-**4h**) in mediate to good yields. Fused and substituted vinyl azides were also accessed to the products (**4i**-**4j**). Notably, aliphatic-substituted substrates could also readily undergo cycloaddition to furnish the target molecules (**4k**-**4n**) in moderate yields with shifty conditions.

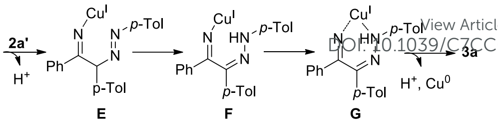
To gain insights into the mechanism of the reaction, we designed series of control experiments in scheme 3. When the amount of BHT was increased to 2.0 equiv, the yield of **3a** sharply decreased to 11% (Scheme 3 a). When 2.0 equiv of TEMPO was added instead of BHT, the reaction generated **3a** with a 30% yield (Scheme 3 a). These results suggest that the transformation may involve a ionic process rather than a radical pathway. Therefore, BHT may provide appropriate acid medium for the decomposition of diazonium salts.

Scheme 3 Mechanistic investigations.



Scheme 4 Proposed Mechanism.





To verify this hypothesis, the reaction was carried out in perence of 0.5 eq. phenol (PhOH) instend of BHT and gave a 50% yield (Scheme 3 a). This result implies that BHT may also offer a protection of Cu(I) from oxidation of oxygen in air except maintaining a certain acidity of reaction system. Furthermore, we introduced *2H*-azirine (**4**) into the reaction with **2a** and obtained desired product **3a** in 40% with 55% recovery of **4** (Scheme 3 b). This result indicates that the reaction may proceed via **4**. We carried out the reaction with enamine substitution **5**[17] and delivered the aimed product **6** in 28% (Scheme 3 c). It suggests the process may include enamine intermidiate.

On the basis of the preliminary data and literature reports,[11,13,18] a plausible mechanism is illustrated in Scheme 4. Initially, the aryl cation **2a''** was delivered from aryldiazonium cation **2a'** with the release of molecular nitrogen in the acidic conditions. Copper-chelated complex **A** from vinyl azide **1a** was then attacked by aryl cation **2a''** to form iminyl metal ions **B**, which could further produce iminyl copper(I) intermediate **C** with elimination of dinitrogen. Alternatively, Consecutive C-N bond cleavage of **4'**, which generates from decomposition of vinyl azide **1a** with help of Cu^I, gives intermediate **C** in the presence of aryl cation **2a''**. This also explains the prolonged reaction time was needed when **1a** was replaced with **4** (Scheme 3 b). Subsequently, tautomerization of **C** provides enamide intermediate **D**, which undergoes addition with aryldiazonium cation **2a'** to afford complexes **E**.[17] The copper-chelate complex **E** could isomerize to the formation of intermediate **F**. Direct reductive elimination of intermediate **E** proceeds and affords final product **3a**.

In conclusion, we developed a flexible cross-coupling and cyclization method through a novel dual-functionalization at the β-carbon of vinyl azides with aryldiazonium salts as double roles, to build structurally diverse N^2-substituted-1,2,3-triazoles. This reaction represents an innovative utilization of vinyl azides and reactive arenediazonium salts and expands the toolbox for conveniently forming three bonds (C-C, C-N and N-N) in one-pot. In addition to tolerating diverse functional groups, the reaction offers the benefit of proceeding under an ambient atmosphere, yielding polyfunctional triazoles in moderate to good yields through readily available substrates. A possible ion mechanism was also proposed. Additional efforts to clearly understand this attractive transformation and the synthesis of other heterocyclic scaffolds are currently ongoing in our group.

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16 CCDC 1525197 (3f) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.

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