Cu(I)-Catalyzed [3+3] Cycloaddition Reaction of Ethynyl Methylene Cyclic Carbamates and Azomethine Imines

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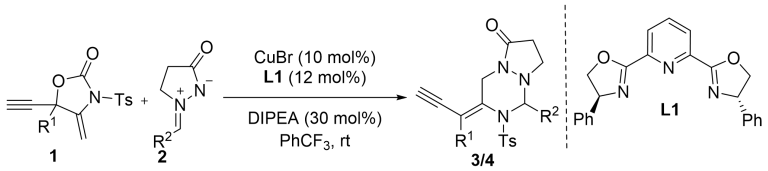


ABSTRACT: A copper-catalyzed efficient, operationally simple, general method for straightforward syntheses of 1,2,4-triazinane derivatives employing EMCCs (ethynyl methylene cyclic carbamates) as precursors reacting with azomethine Imines was firstly reported. A wide variety of 1,2,4-triazinane derivatives were obtained in acceptable to good yields under mild conditions. This protocol features broad substrate scope, high functional group tolerance and easy operation, therefore enabling late-stage functionalization. In addition, a scale-up experiment further highlighted the synthetic utility.

The 1,2,4-triazinane and 1,2,4-triazinane derivatives, an important class of six-membered-ring heterocycles, have exhibited a variety of pharmacological and biological activities applied to pharmaceutical candidates (Figure 1).[1] For example, **E-7386** is an orally active CBP/β-catenin modulator, exhibiting significant anti-tumor activity.[2] Cyclic amidoxime **I** derivatives are used to treat thromboembolism because of their anticoagulant effect (Figure 1).[3] As a therapy for uric acid diathesis, the pyrazolo[1,2-a][1,2,4]triazine-1,3-dione xanthene oxidase inhibits **II** (Figure 1).[4] Accordingly, the broad biological activities and attractive physicochemical properties of ,2,4-triazinanes, as well as their industrial relevance have aroused great interest among chemists, and new synthetic methods for these compounds occupy an important field in synthetic organic chemistry. Some examples of synthetic 1,2,4-triazinane derivatives are shown below: Wang's group presented the first cross-1,3-dipolar cycloaddition reactions between pyrazolidinium ylides

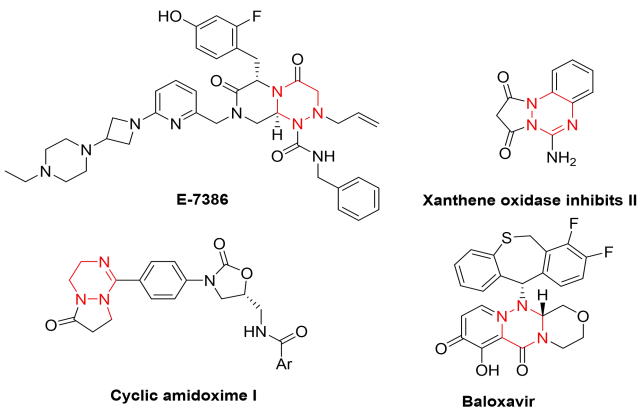
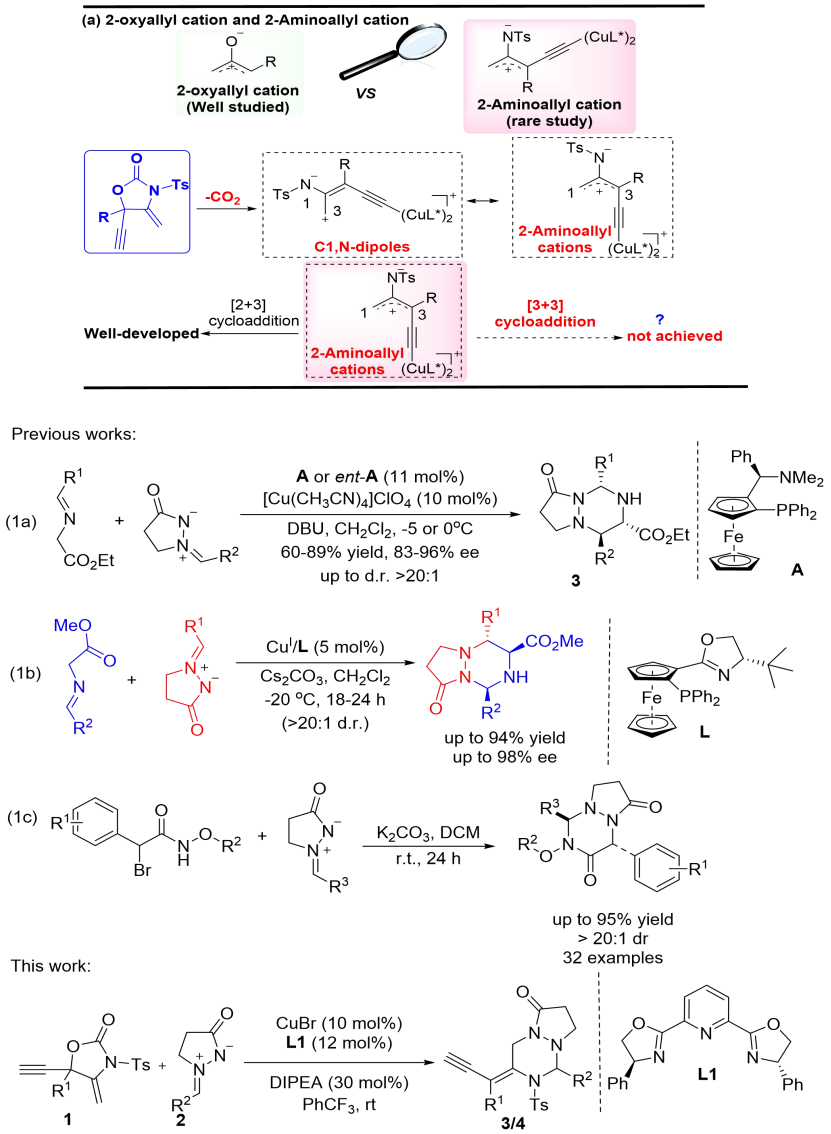


Figure 1. Selected biologically active natural products and drug molecules with 1,2,4-triazinane skeleton.

and azomethine ylides employing the Cu^{I}/^{t}Bu-Phosferrox complex as the catalyst in 2013 (1a, Scheme 1). A wide range of 1,2,4-triazinane derivatives having a diversity of functional groups were realized in generally high yield with excellent stereocontrol.[5] Almost at the same time, Guo's group developed a copper-catalyzed highly diastereo- and enantioselective [3+3] cycloaddition of azomethine ylides with azomethine imines in the presence of ferrocenyl P, N chiral ligands (1b, Scheme 1).[6] In addition, Peng's group have successfully developed a methodology to access pyrazolone-fused 1,2,4-tria zines by the [3+3] cycloaddition reaction of azomethine imines with in situ-formed azaoxyallyl cations(1c, Scheme 1).[7] Despite these impressive achievements, the development of efficient protocols to synthesize 1,2,4-triazinane derivatives are still in great demand for further biological evaluations.

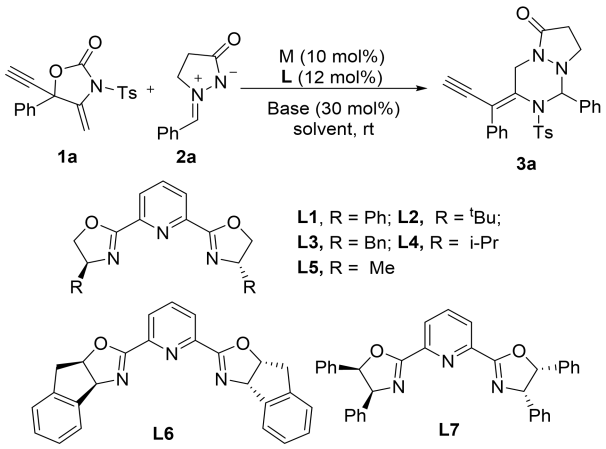
Scheme 1. Reactions of azomethines with 2-aminoallyl cations featuring 1,2,4-triazinane derivatives.



Over the past several decade, many achievements have been made in the cycloaddition reaction of 2-oxoallyl cations.[7-8] However, to our knowledge, 2-aminoallyl cations are analogues of 2-oxoallyl cations that have existed for over 40 years, and there are few reports on their cycloaddition reactions, mainly because the production of this substance usually requires harsh

conditions.[9] Recently, the Zi's group disclosed a decarboxylation strategy for the formation of 2-aminoallyl cation using ethynylmethylenecyclic carbamate (EMCC).[10] Good research results have been achieved in the construction of polycyclic heterocyclic compounds by incorporating azo zwitterions into the cycloaddition reactions of cyclic and acyclic dienyl silyl ethers or indoles.[11] As a continuation of our interest in the development of new methods for constructing heterocycles,[12] herein we reported a new method for synthesizing 1,2,4-triazinane derivatives via Cu(I)-catalyzed reaction of ethynyl methylene cyclic carbamates and azomethine imines for the first time.

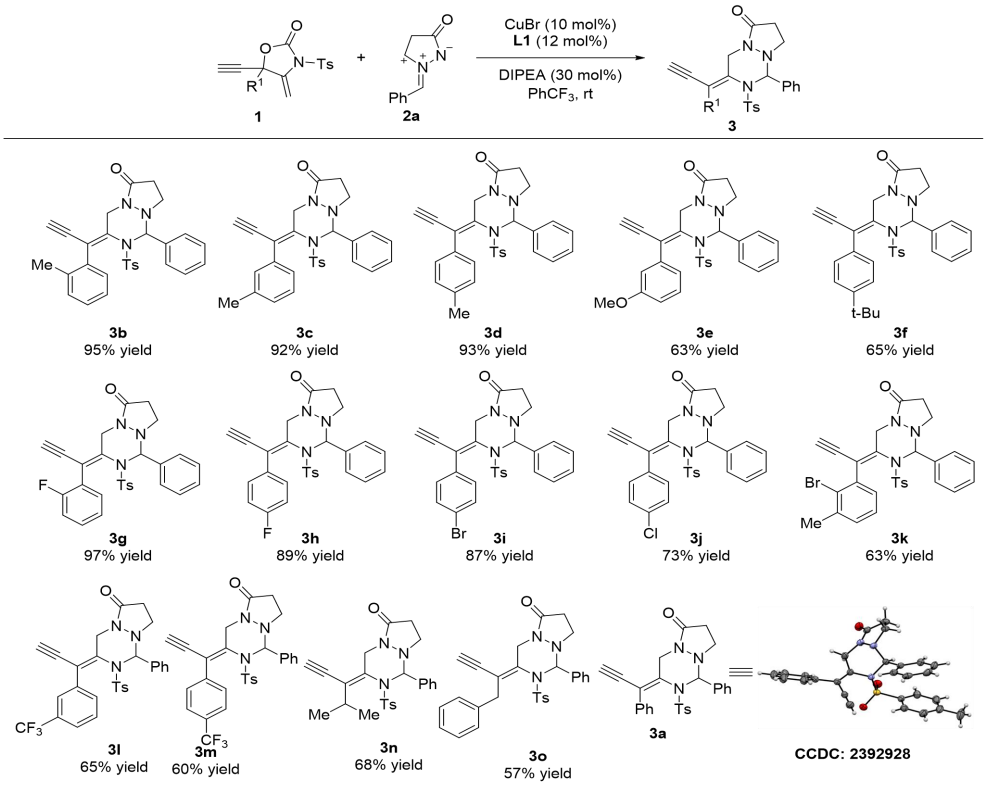
Table 1. Optimization of the Reaction Conditions[a]



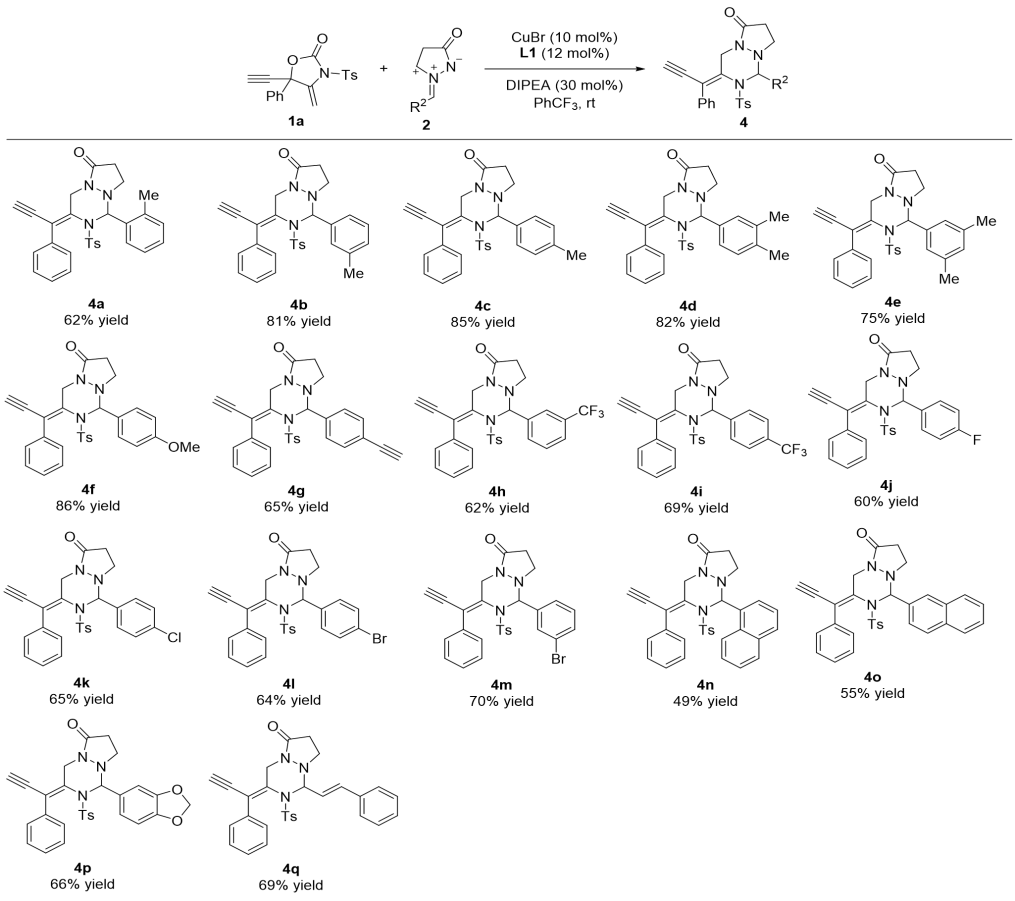
entry	M	ligand	base	solvent	yield (%)[b]	ee (%)[c]
1	CuOTf	L1	DIPEA	$PhCF_3$	65	28
2	CuOTf	L2	DIPEA	$PhCF_3$	22	0
3	CuOTf	L3	DIPEA	$PhCF_3$	35	0
4	CuOTf	L4	DIPEA	$PhCF_3$	46	0
5	CuOTf	L5	DIPEA	$PhCF_3$	12	0
6	CuOTf	L6	DIPEA	$PhCF_3$	38	0
7	CuOTf	L7	DIPEA	$PhCF_3$	56	20
8	CuI	L1	DIPEA	$PhCF_3$	62	/
9	$CuBF_4$	L1	DIPEA	$PhCF_3$	34	/
10	CuOAc	L1	DIPEA	$PhCF_3$	65	/
11	CuBr	L1	DIPEA	$PhCF_3$	89	/
12	CuCl	L1	DIPEA	$PhCF_3$	82	/
13	$Cu(OTf)_2$	L1	DIPEA	$PhCF_3$	27	/
14	$CuPF_6$	L1	DIPEA	$PhCF_3$	63	/
15	Cu(OAc)2	L1	DIPEA	$PhCF_3$	55	/
16	CuTC	L1	DIPEA	$PhCF_3$	44	/

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.4 mmol), N_2 atmosphere, M (10 mol%), L (12 mol%), DIPEA (30 mol%), $PhCF_3$ (2.5 mL). [b]isolated yield. [c]Determined by chiral HPLC analysis.

Scheme 2. Substrate scope with respect to the EMCCs **1**.[#]



Scheme 3. Substrate scope of azomethine imines **2**.[#]



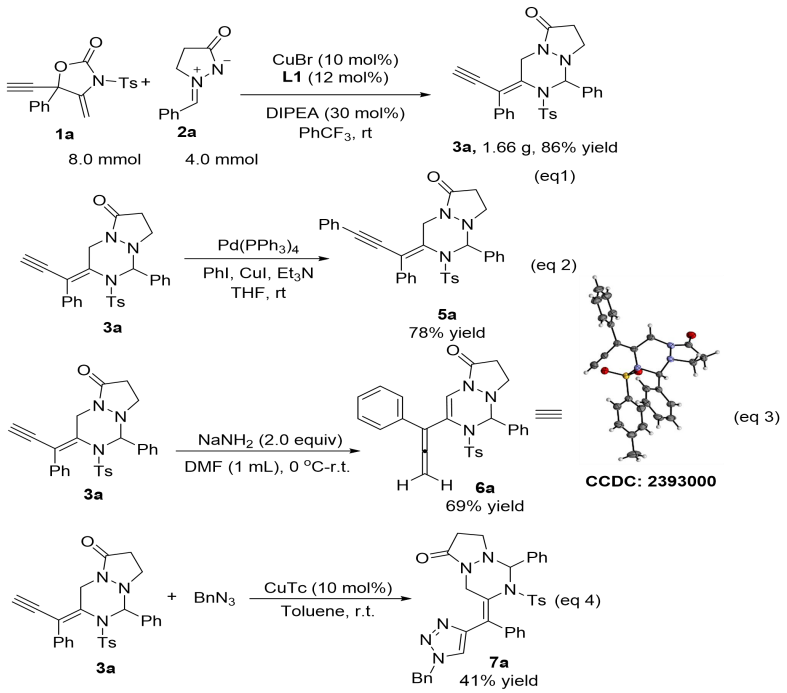
To commence our studies, we initially, selected EMCC **1a** with azomethine imine **2a** as model substrates in the presence of 12 mol% of L1 with 10 mol% CuOTf with 30 mol% DIPEA in $PhCF_3$ at room temperature. To our delight, PyBOX ligand **L1** showed average showed average catalytic ability, affording **3a** in 65% yield with 28% ee (Table 1, entry 1). To further confirm the chemical structure of **3a**, we conducted single-crystal X-ray diffraction analysis (for details see the supporting information). Next, a series of PyBOX ligands **L2-L7** were evaluated to test the reaction, the desired product **3a** was obtained in low yields (22-56%) and only 20% ee. In order to improve the yield, we turn to screening different solvents or bases and find that using $PhCF_3$ and DIPEA to deliver **3a** with good yield (for details, see the Supporting Information). Further screening of copper salts and find that using CuBr to deliver **3a** with good yield (89%).

With the optimized reaction conditions in hand (Table 1, entry 11), a variety of EMCCs were employed to test the generality of this process. Fortunately, A series of EMCCs participating in the reaction bearing phenyl groups with various substituents at different positions (para, meta or ortho) showed good to excellent yields (60-95%) whether the substituent was electrondonating (**3b-3f**: -Me, -OMe, -t-Bu) group or electron-withdrawing group (**3g-3m**: -F, -Cl, -Br, $-CF_3$). When **R1** was an alkyl group (i-Pr or Bn), corresponding products **3n** and **3o** were also obtained in good yields (57-68%).

Further investigation of the substrate scope of azomethine imines **2** were employed to test the generality of this reaction process. Firstly, azomethine amines **1** with electron-donating substituted phenyl ring (para, meta or ortho) were evaluated, and in all case (**4a-4f**), good to high yields (62-86%) were achieved. In addition, the introduction of electron-withdrawing groups such as acetylene group, -F, -Cl, -Br and $-CF_3$ substituents on the phenyl rings also afforded the corresponding products (**4g-4m**) in 65-70% yields. The substrates with naphthyl (**4n-4o**) or hetero-aromatic (**4p**) substituents worked well, affording **4n-4p** in 49-66% yields. Moreover, azomethine amine **1** containing styryl success fully reacted with EMCC **2a**, furnishing the desired products **4q** in 57% yields.

To illustrate the potential application of current protocol, a gram-scale reaction of EMCC **1a** (8.0 mmol) with azomethine imine **2a** (4.0 mmol) was conducted in the presence of CuBr (10 mol%), **L1** (12 mol%), DIPEA (30 mol%) as catalyst in $PhCF_3$ (eq 1, Scheme 4). Gratifyingly, the reaction proceeded smoothly to afford **3a** in 86% yield (1.66 g). Next, **3a** could be easily transferred to **6a** via Sonogashira coupling reaction in 78% yield (eq 2, Scheme 4). Under strong alkaline conditions, **3a** can be converted into diene product **6a** (eq 3, Scheme 4). Moreover, a copper-catalyzed azide-alkyne cycloaddition (Cu-AAC) reaction of **3a** with benzyl azide afforded the corresponding triazole **7a** in 41% yield (eq 4, Scheme 4).

Scheme 4. Gram-scale experiments of product **3a** and transformation



Scheme 5. Control experiments.

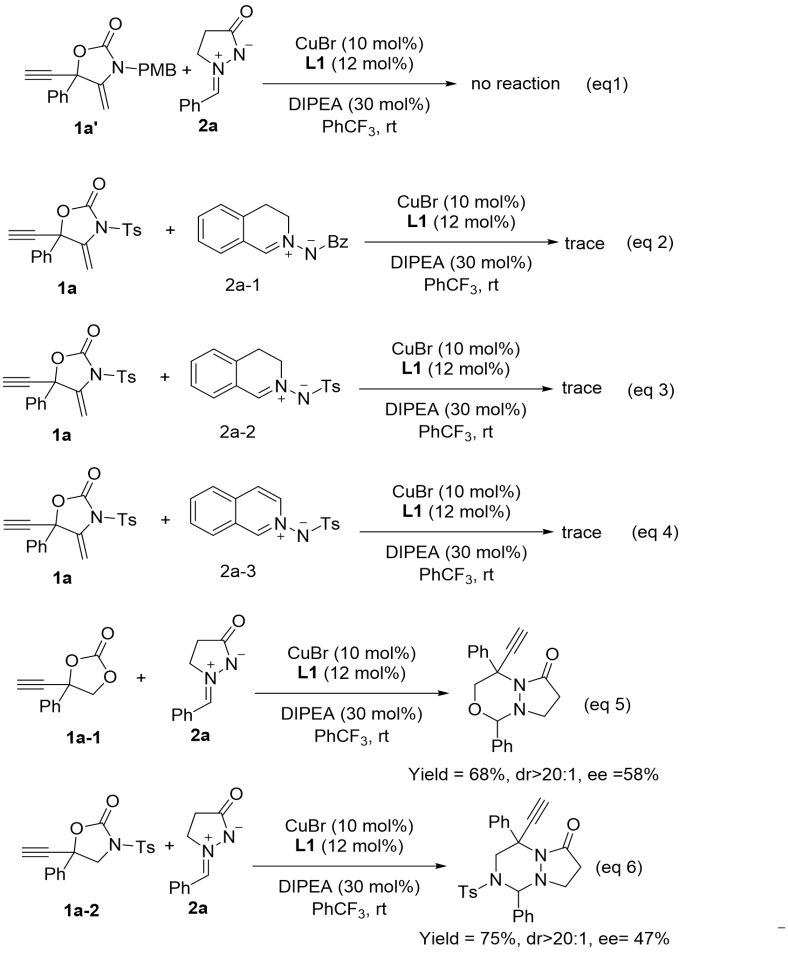
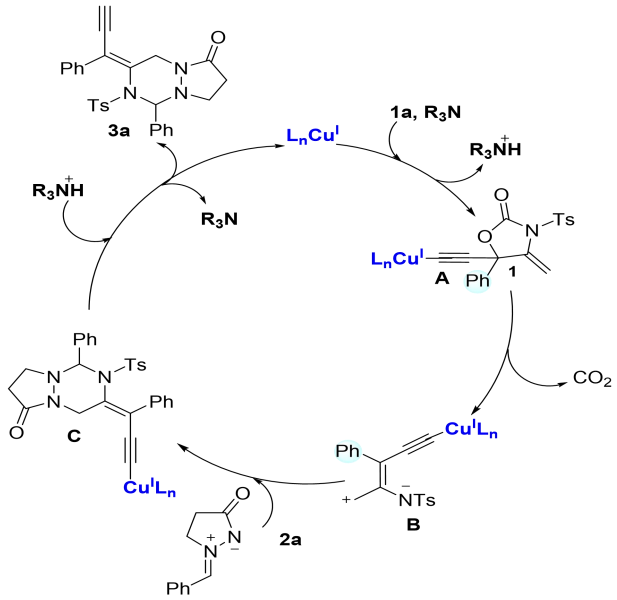


Figure 2. Postulated Mechanism.



To study the diversity of substrates, we replaced **1a** with **1a'**, we were unable to obtain product **3a'** (eq 1, Scheme 5). Next, we examined different types of 1,3 dipoles (**2a-1, 2a-2, 2a-3,** eq 2-4, Scheme 5) and obtained trace product. In addition, we also studied different types of alkyne substrates (**1a-1,1a-2**)(eq 5-6, Scheme 5), which can only achieve general yields and enantioselectivity. The proposed mechanism for this reaction was exhibited in Figure 2. Under the effect of DIPEA, EMCC **1a** coordinated with $LnCu^{I}$ to form the copper-acetylide complex **A**. Copper-assisted propargylic decarboxylation then occured to produce the 2-aminoallyl cation with C1,N-dipolar form **B**. Then, azomethine imine **2a** reacted with **B** to generate **C**. Subsequently, **C** underwent intramolecular cyclization to obtain **3a**, while copper was released undergoing protodemetalation by R_3NH^+ and restarted a new catalytic cycle.

In summary, we have demonstrated an efficient, facile and practical one-pot procedure for the synthesis of 1,2,4-triazinane derivatives catalyzed by Cu(I) complexe using EMCCs as precursors for generating 2-aminoallyl cations. A wide variety of 1,2,4-triazinane derivatives were obtained in acceptable to good yields under quite mild conditions. In addition, a scale-up experiment and the synthetic transformations of the 1,2,4-triazinane derivatives further highlighted the synthetic utility. Further research on the development of new type of Cu(I) complexes and its application in asymmetric reactions about EMCCs are ongoing in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectroscopic data (PDF)

Accession Codes

CCDC 2392928 and 2393000 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, 196 Cambridge CB2 1EZ, UK; fax:

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Notes

The authors declare no competing financial interest.

[#]Reaction conditions: **1** (0.40 mmol), **2** (0.20 mmol), CuBr (10 mol %), L1 (12 mol %), DIPEA(30 mol%) in $PhCF_3$ (2.5 mL) at rt under N_2 atmosphere. **3** or **4** isolated yields.

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