RESEARCH ARTICLE

Check for updates

Prolinamide plays a key role in promoting copper-catalyzed cycloaddition of azides and alkynes in aqueous media *via* unprecedented metallacycle intermediates†

Gargi Chakraborti, Rajkumar Jana, Tirtha Mandal, Ayan Datta [ID] * and Jyotirmayee Dash [ID] *

We herein delineate cycloaddition of a wide range of azides with terminal alkynes using catalytic CuI and a prolinamide ligand in aqueous media under aerobic conditions. The catalytic system is used for a 'one-pot' synthesis of triazoles from aliphatic halides and alkynes. A detailed computational study predicts that prolinamide plays a unique role in facilitating the cycloaddition in water *via* the formation of remarkable metallacycle intermediates. The synthetic utility of the method is demonstrated by the synthesis of pharmacologically relevant triazolyl diaryl amines *via* a Cu(I) catalyzed relay cycloaddition and Ullmann coupling sequence.

Introduction

The Cu(I) catalyzed Huisgen[1] 1,3-dipolar cycloaddition[2] of organic azides with alkynes is referred to as the prototypical 'click reaction' that has found diverse applications in fields ranging from medicinal chemistry to materials science.[3,4] While the Huisgen reaction produces a mixture of 1,4- and 1,5-disubstituted triazole products in most cases,[1] Sharpless[5a] and Meldal[5b] independently reported copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) to obtain 1,4-disubstituted 1,2,3-triazoles regiospecifically. Triazole derivatives are privileged scaffolds in medicinal chemistry, showing potent anti-cancer, anti-allergic, anti-bacterial, and anti-HIV activities.[6,7] In our group, we have been using Cu(I) catalyzed and target directed azide–alkyne cycloaddition to prepare triazole ligands for DNA secondary structures with potent biological activities.[7]

Numerous strategies based on Cu(I) based catalytic systems[8] have been developed to efficiently synthesize triazole products.[9,10] In some instances, high temperature or microwave conditions are required for copper(I) iodide catalyzed cycloadditions. However, the reaction can be performed at room temperature using Cu(I) in the presence of nitrogen, sulfur, NHC or polydentate ligands.[11–14] Finn *et al.* reported that tris(2-benzimidazolylmethyl)amine ligands can accelerate copper(I)-catalyzed azide–alkyne cycloaddition with substantial improvements in the reaction rate as well as in yields of the triazole products.[11a]

Reiser *et al.* used a heterogeneous copper(I) isonitrile complex as an efficient catalyst for the 1,3-dipolar cycloaddition of azides and alkynes under mild conditions in water (Scheme 1).[9h] Díez-González *et al.* reported cycloaddition of azides and alkynes using the commercially available complex [CuBr(PPh₃)₃] under neat conditions.[9i] Although these methods have been widely used for the synthesis of triazoles from alkyl azides and alkynes, cycloaddition between substituted aromatic azides and alkynes in an aqueous environment under ambient conditions still remains challenging.

In this context, we herein describe Cu(I) catalyzed azide–alkyne cycloaddition in aqueous media at room temperature using a triazolyl–prolinamide ligand, **Pro-1** (Scheme 1). The reaction proceeds with low Cu(I) and **Pro-1** loading (5 mol% CuI and 10 mol% **Pro-1**), providing highly pure triazole products in excellent yields, even obviating the need for column chromatographic purifications. Cu(I) salts have been directly used as catalysts in cycloaddition using polydentate nitrogen ligands that stabilize Cu(I) intermediates and accelerate the reactions.[9,11–14] Inspired by this fact, we successfully employed the triazolyl–prolinamide **Pro-1** as a ligand for CuAAC reactions (Scheme 1). The ligand contains two complementary hydrophobic and hydrophilic functional groups, which makes it ideal for assisting the reaction in aqueous media.[15] It is further intriguing to find the role of **Pro-1** in the catalytic cycle as well as in the transition state of CuAAC using DFT studies. Moreover, the synthetic utility has been demonstrated *via* a relay CuAAC–Ullmann coupling process.

School of Chemical Sciences, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India. E-mail: spad@iacs.res.in, ocjd@iacs.res.in
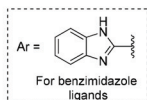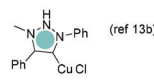†Electronic supplementary information (ESI) available. See DOI: 10.1039/d0qo01150a

2434 | *Org. Chem. Front.*, 2021, **8**, 2434–2441

This journal is © the Partner Organisations 2021
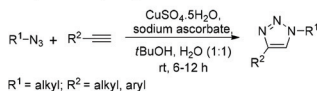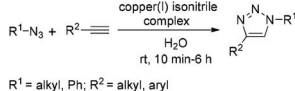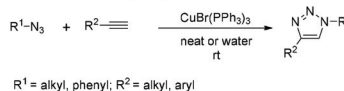
Scheme 1 Synthesis of triazole derivatives using CuAAC of azides and alkynes.

Results and discussion

We commenced our studies with the CuAAC of *p*-azidoanisole (**1a**) with phenylacetylene (**2a**) as the model reaction at room temperature in aqueous media (Table 1; see Tables S1 and S2 in ESI,† for the detailed optimization study). To our delight, the reaction proceeded satisfactorily providing the desired product **3a** in 95% yield (entry 1, Table 1). Later, DFT calcu-

lations revealed that water is an excellent solvent for the reaction to occur at room temperature (Fig. 1 and 2). Further, **Pro-1** was found to be the optimal ligand for this transformation, indicating that the structure of prolinamide derivatives may be crucial for attaining high catalytic reactivity (entry 1).[16] The synthetic details of prolinamide ligands (**Pro-1**, **Pro-2**, and **Pro-3**) are given in the ESI (Schemes S1–S5, ESI†). The reaction of *p*-azidoanisole (**1a**) with phenylacetylene (**2a**) proceeded satisfactorily in the presence of 5 mol% CuI and 10 mol% **Pro-1**. However, when the reaction was performed using half the loading of **Pro-1**, the yield of the triazole derivative **3a** decreased (65%, Table S2†).

With the optimized reaction conditions (0.1 equiv. **Pro-1**, 0.05 eq. CuI, in 0.1 M water at room temperature; Table 1, entry 1), we next explored the scope of the reaction by varying azides and acetylenes (Schemes 2 and 3). It is worth noting that only a few studies on CuAAC of aromatic azides have previously been reported in aqueous media at room temperature.[9,10]
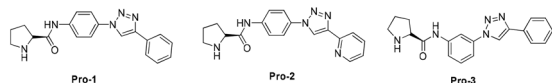
We were pleased to find that a variety of aromatic azides containing both electron-rich and electron-deficient functional groups (alkyl, methoxy, nitrile, nitro, ketone and halogen as substituents) reacted efficiently providing triazole products in excellent yields and high purity (**3a–3z**, Scheme 2). The *ortho*- and *meta*-substituted aromatic azides also provided the corresponding triazole products in high yields (92–95%, Scheme 2). Importantly, aryl azides containing hydroxy and amine substituents afforded the desired products (**3b**, **3c**, **3u** and **3v**) in excellent yields (90–94%).

The viability of this catalytic protocol was next expanded using aliphatic, aromatic and heteroaromatic azides, nucleoside derived azides, and bis-azides as well as different aryl, alkyl and heteroaromatic alkynes **2a**, **2s**, **2x** and **5a–d** (Scheme 3). Aliphatic azides furnished the corresponding

Table 1 Optimization of reaction conditions[a]

Entry	Ligand	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	**Pro-1**	**CuI**	**H₂O**	**8**	**95**
2	—	CuI	H₂O	48	20
3	**Pro-1**	—	H₂O	12 h	n.r.
4	DMEDA	CuI	H₂O	8	40
5	Phenanthroline	CuI	H₂O	8	51
6	ʟ-Proline	CuI	H₂O	8	65
7	**Pro-2**	CuI	H₂O	8	68
8	**Pro-3**	CuI	H₂O	8	40
9	**Pro-1**	Cu(OAc)₂	H₂O	8	21
10	**Pro-1**	CuO	H₂O	8	—
11	**Pro-1**	CuBr	H₂O	8	57
12	**Pro-1**	Cu(0)	H₂O	8	—

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.50 mmol), CuI (0.05 mmol), **Pro-1** (0.1 mmol) in 2 mL water. [b] Yield refers to the isolated yield without chromatographic purification.

This journal is © the Partner Organisations 2021

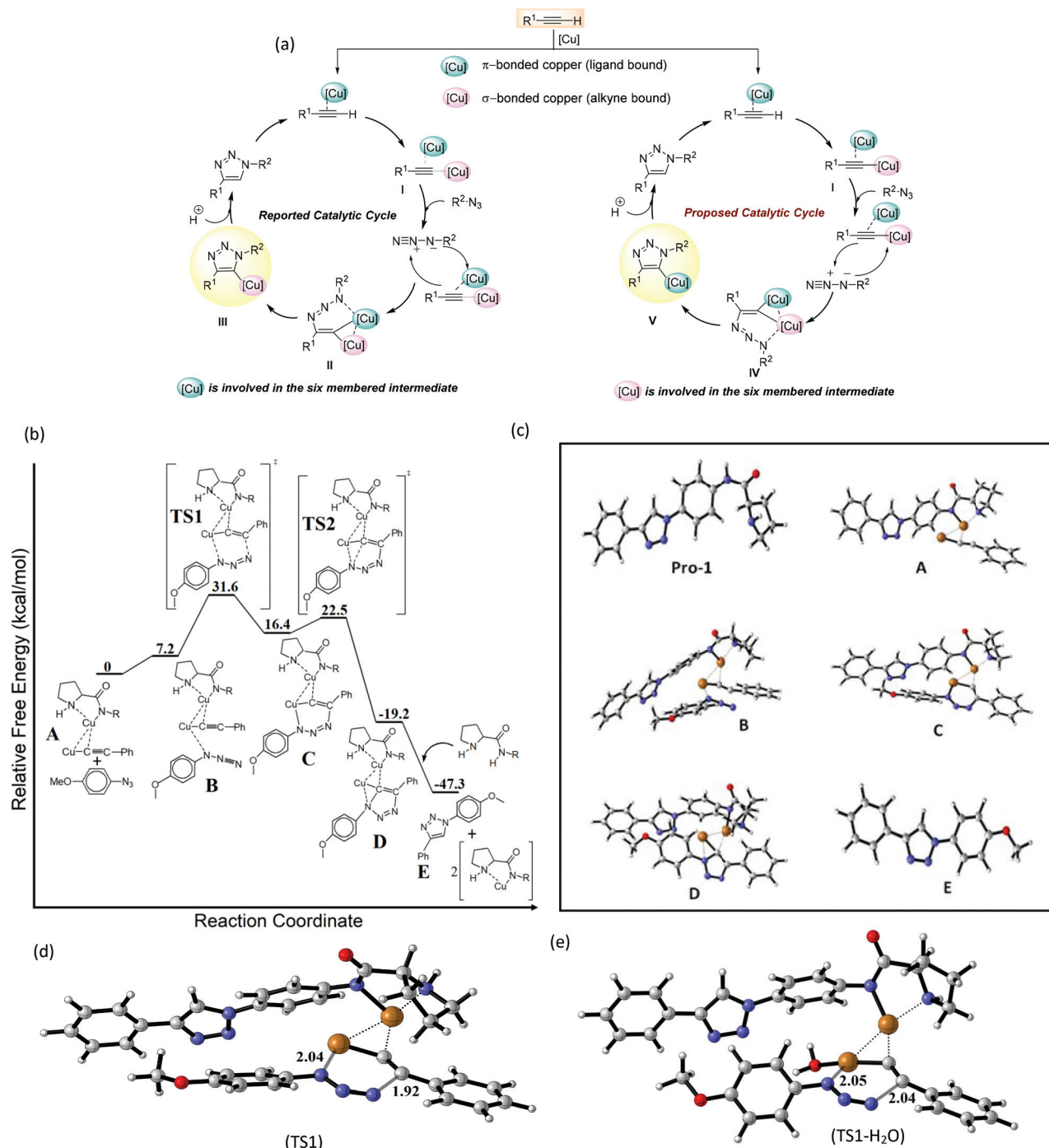*Org. Chem. Front.*, 2021, **8**, 2434–2441 | **2435**

Fig. 1 (a) Comparison between Fokin's mechanism and our proposed mechanistic model of CuAAC. (b) Free energy profile for the binuclear CuAAC reaction. (c) Optimized structures of all the reaction intermediates, reactants, products and catalysts for the CuAAC reaction. Optimized transition state (TS) structures with select bond lengths (in Å). (d) TS1 of the cycloaddition. (e) TS1 with the coordinated water molecule (explicit model).

cycloaddition products (**6a–6h**) in 78%–96% yields (Scheme 3). The aromatic bis-azide **4b** also produced the desired bis-triazole product **6g**. Thus, the method can be used for the synthesis of both mono- and bis-triazole derivatives. Heteroaromatic azides such as thiazole azide **4d** and coumarin azide **4e** reacted with phenylacetylene **2a** to provide the corresponding triazoles (**6i** and **6j**) in high yields (Scheme 3).

Importantly, guanosine azide **4f** could be coupled with alkynes **2a** and **5d** under the aqueous conditions to afford the products **6k** and **6l** in 74–77% yields (Scheme 3). Previously, the triazolylnucleobase derivatives were synthesized by CuAAC under a long reaction time.[17] The present method offers an efficient approach for synthesizing nucleobase derived triazoles under mild reaction conditions in high yields. Aliphatic
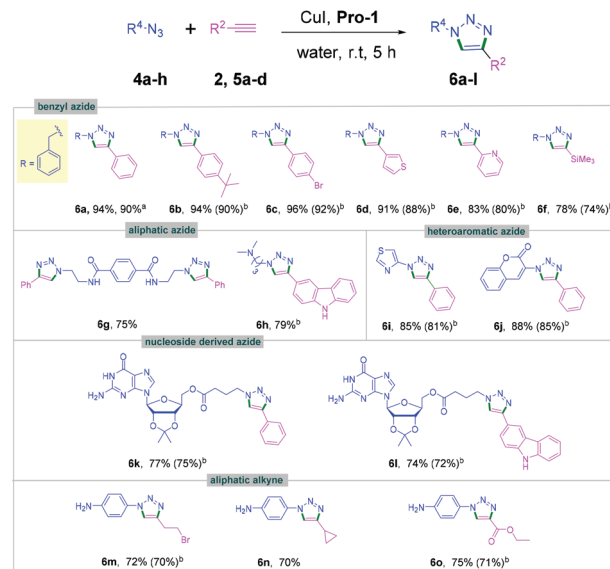
Fig. 2 Solvent dependent variation of activation energies for the rate-determining TS.
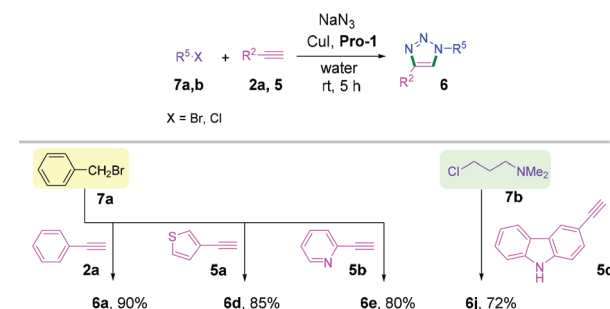

Scheme 2 Cycloaddition of aromatic azides and alkynes: [a]reaction performed with 1 g of **1a** for 8 h, [b]isolated yields after chromatographic purification.

Scheme 3 Reaction of benzyl, aliphatic, heteroaromatic and nucleo-base derived azides with aromatic and aliphatic alkynes, [a]reaction performed with 1 g of **1a** for 5 h, [b]isolated yields after chromatographic purification.

Scheme 4 One-pot synthesis of triazoles from alkyl halides.

alkynes were also found to be compatible under the optimized conditions providing the desired triazoles **6f** and **6m–o** in good yields (Scheme 3). Gram-scale experiments with 1 g each of **1a** and **4a** were successfully performed affording the corresponding triazoles **3a** and **6c** in excellent yields (Schemes 2 and 3).

We next examined this protocol for a one-pot sequential synthesis of triazoles from benzyl/alkyl halides. Benzyl/alkyl halides **7a,b** were converted to the corresponding azides *in situ* and then reacted with terminal alkynes **2a**, **5a**, **5b** and **5d**

(Scheme 4 and Table S3, ESI†). Triazole derivatives **6** were obtained with excellent yields without any chromatographic purification (Scheme 4). However, we failed to isolate any triazole products when the one-pot reaction was performed using aromatic bromides.[18]

The well-established catalytic model for CuAAC developed by Fokin *et al.* suggested that the σ-bound copper acetylide coordinates to an organic azide *via* the π-bound enriched copper atom to produce complex **I** (Fig. 1a).[19] Next, the nucleophilic attack at *N*-3 of the azide by the β-carbon of the acetylide forms an unusual six-membered copper metallacycle **II**, containing the π-bound copper atom. Ring contraction of the intermediate **II** then provides triazole **III** containing the σ-bound copper atom.

Intriguingly, a bulky Cu-**Pro-1** complex is generated similar to N-heterocyclic Cu catalysts reported by Chen *et al.*[20,21] Owing to the bulky nature of the complex, the azide is stereochemically locked in a particular fashion, *i.e.* from below the

molecular plane of the Cu-**Pro-1** complex (Fig. 1a). The conformation of **Pro-1** forces the orientation of the intermediate in such a way that the σ-bound copper atom is involved in the six membered metallacycle **IV**. Intermediate **IV** then leads to the formation of triazole **V** that contains the π-bound copper atom. Protonolysis of **V** provides the desired triazole derivative.

In order to gain insight into the reaction mechanism, density functional theory (DFT) studies were performed using the Gaussian 16 suite of programs[22] (the details of the calculations are provided in the ESI† in the "General information on computational methods" section). The CuAAC was expected to be initiated through the activation of **Pro-1** by CuI with the formation of the Cu-**Pro-1** catalytic complex and deprotonation of phenylacetylene to form a Cu acetylide. Subsequently, the formation of an intermediate (**A**) occurred *via* Cu···Cu and Cu···C weak interactions between Cu-**Pro-1** and Cu acetylide (Fig. 1b and c). The succeeding cycloaddition between *p*-azidoanisole and Cu-**Pro-1**–acetylide proceeded through the weak bonding interaction between the Cu atom of the acetylide and the nitrogen of the azide (Cu···N) (intermediate **B**). According to previous literature studies, the reaction barriers for a binuclear path of cycloaddition are lower than those for a mononuclear one.[20,23–26] We have synthesized a Cu-acetylide using phenyl acetylene and used it to carry out the cycloaddition in the presence of **Pro-1**. It was observed that the kinetics of this mononuclear pathway proceeded slowly under the optimized reaction conditions (for details see ESI Scheme S8 and Table S5†). Therefore, the most accepted binuclear mechanism was used as a framework to investigate our method.

The cycloaddition step for the formation of six membered metallacycle is considered to be the rate-determining step for Cu-catalyzed alkyne–azide cycloaddition reaction.[20,23,25] The estimated activation energy barrier for the cycloaddition was 24.4 kcal mol^{-1} (TS1, Fig. 1a and 2), which agrees well with the earlier studies.[20,23] However, the activation energy for a mononuclear cycloaddition pathway was estimated to be 30.5 kcal mol^{-1} (Fig. S1†), which is relatively higher than that for a binuclear pathway. Therefore, even though the possibility of a mononuclear reaction pathway cannot be directly ruled out, cycloaddition preferably proceeds through a binuclear pathway. The structure of the optimized transition state (TS1, Fig. 1b) exhibits a bond forming interaction between the carbon atom of the acetylide and the nitrogen atom of the azide (C···N) with a bond distance of 1.92 Å. Again, a Cu···N interaction (with 2.04 Å bond distance) is also present in the TS forming a six-membered ring. The formation of the six-membered metallacycle (intermediate-C and intermediate IV) in a stereochemically locked configuration is the key difference between our proposed and the earlier reported catalytic cycle. The previously reported mechanism describes the formation of a six-membered metallacycle *via* the bonding interaction between the π-bound copper and azide N-3 atom while in this case, the interaction occurs between the σ-bonded Cu and azide N-3 atom. However, the resultant six-membered metallacycle is both kinetically and thermodynamically unstable. Hence, it rapidly undergoes ring contraction to form a more

stable five-membered [Cu-**Pro-1**][(1-*para*-methoxyphenyl-4-phenyl-1,2,3-triazol-5-yl-Cu] complex (D) with a very low activation barrier of 6.1 kcal mol^{-1} (Fig. 1b and S2†). In the optimized transition state (TS2) leading to the formation of the five membered ring, the bonding interaction between the nitrogen of the azide and the carbon of the acetylide starts forming with a 1.98 Å bond distance (Fig. S2a†).

In order to mimic the experimental conditions, an SMD model was adopted with water, dimethyl sulfoxide and benzene as the continuum dielectrics (ε = 78.35, 46.83 and 2.27 respectively) and the corresponding energy activation barriers for transition states were determined. It was observed that the TS structures were stabilized in the presence of polar solvents, especially water, while for nonpolar solvents like benzene, there was a substantial increase in activation energy barriers. The activation barriers for TS1 are 24.4, 8.3, 14.1, and 20.5 kcal mol^{-1} respectively for the gas phase, water, DMSO and benzene (Fig. 2). A similar trend was also observed for TS2 with activation barriers of 6.1, 2.7, 3.6 and 4.8 kcal mol^{-1} respectively (Fig. S2†). Besides the implicit model, we have also considered the explicit solvation model to get a more accurate energy activation barrier as well as transition state structures. The coordination of solvent molecules (namely water, THF, and acetonitrile) with the σ-bonded copper has been reported to accelerate the reaction by stabilizing the transition state structures.[23,25] In the explicit model, the effect of coordination of water molecules in the rate-determining transition state is studied (Fig. 1e). As in the implicit model, there is a substantial decrease in activation barrier (11.9 kcal mol^{-1}) for the cycloaddition step. This reduction in energy activation barrier in the presence of a solvent can be attributed to the transition state stabilizing effect of the water molecule by coordinating to σ-bonded alkyne-Cu through the formation of a strong Cu–O bond. This observation nicely corroborates with the earlier studies.[23,25] This study indicates that water, a polar protic solvent, not only is beneficial for the protonation of intermediates for the formation of the product but also substantially stabilizes the transition state through a strong Cu–O bonding interaction and hence water is an excellent solvent for this cycloaddition reaction. Even though the reaction might proceed in a polar aprotic solvent like DMSO, nonpolar solvents like benzene would retard the rate of reaction to a greater extent. This result very nicely corroborates with experimental studies. In the final step of cycloaddition, complex (D) is protonated by neighbouring **Pro-1** to afford the corresponding triazole product (E) and two Cu-**Pro-1** complexes were regenerated. This process was estimated to be more exoergic by 28.1 kcal mol^{-1}. Thus, computational studies reveal in detail the mechanistic pathways for the cycloaddition of azides and alkynes and explain why water as a solvent facilitates this room temperature CuAAC process.

Next, we envisioned that the Ullmann type reaction[15c,27] and cycloaddition be combined to develop a new relay process[28] in a single reaction vessel, providing a class of triazolyldiaryl amine derivatives. Relay processes combine multiple steps in one-pot and significantly reduce reaction time, energy

2438 | *Org. Chem. Front.*, 2021, **8**, 2434–2441

This journal is © the Partner Organisations 2021
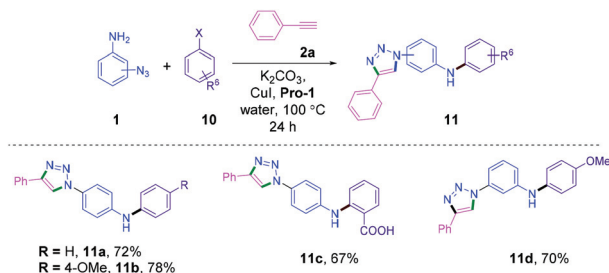
Scheme 5   Relay Ullmann–CuAAC.

and waste of materials.[29] The reactions of azidoanilines **1**, alkyne **2** and aryl halides **10** were performed in a single pot in the presence of the CuI-**Pro-1** catalytic system. The catalytic system efficiently promoted the relay process to provide triazolyldiaryl amines **11a–d** in good to excellent yields (Scheme 5 and Table S4, ESI†).

Conclusions

In summary, we have developed azide–alkyne cycloaddition (AAC) in aqueous media at room temperature using CuI and a prolinamide ligand. The reaction is compatible with many functional groups, thereby enabling the synthesis of 1,4-disubstituted triazoles with diverse structural features. Importantly, the present catalytic system can be readily applied for the one-pot three-component preparation of triazoles using alkyl halides under relatively mild conditions. Furthermore, a Cu(ɪ) catalyzed relay AAC and C–N bond formation is delineated providing an easy access to triazolyl diaryl amine derivatives. The reaction mechanism has been studied by detailed DFT analysis, which indicates the formation of unique metallacycles containing the ligand bound copper atom and further provides evidence that water is the best solvent. The robustness of the catalyst system, broad substrate scope, mild conditions, wide applicability and a different mechanistic approach render the method expeditious for the practical synthesis of triazole derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 (*a*) R. Huisgen, 1,3-Dipolar Cycloadditions. Past and Future, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565–598; (*b*) R. Huisgen and A. Padwa, in *1,3-Dipolar Cycloaddition Chemistry*, ed. Wiley, New York, 1984, pp. 1–176.

2 (*a*) B. M. Trost and I. Fleming, in *Comprehensive Organic Synthesis*, ed. Pergamon, Oxford, 1991, vol. 4, pp. 1069–1109; (*b*) T. Hashimoto and K. Maruoka, Recent Advances of Catalytic Asymmetric 1,3-Dipolar Cycloadditions, *Chem. Rev.*, 2015, **115**, 5366–5412; (*c*) L. Maiuolo, V. Algieri, F. Olivito and A. De Nino, Recent Developments on 1,3-Dipolar Cycloaddition Reactions by Catalysis in Green Solvents, *Catalysts*, 2020, **10**, 65–92; (*d*) M. Breugst and H.-U. Reissig, The Huisgen Reaction: Milestones of the 1,3-Dipolar Cycloaddition, *Angew. Chem.*, 2020, **59**, 12293–12307 and the references therein.

3 H. C. Kolb, M. G. Finn and K. B. Sharpless, Click Chemistry : Diverse Chemical Function from a Few Good Reactions, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021.

4 For reviews, see: (*a*) S. K. Mamidyala and M. G. Finn, In situ click chemistry: probing the binding landscapes of biological molecules, *Chem. Soc. Rev.*, 2010, **39**, 1252–1261; (*b*) K. D. Hanni and D. A. Leigh, The application of CuAAC 'click' chemistry to catenane and rotaxane synthesis, *Chem. Soc. Rev.*, 2010, **39**, 1240–1251; (*c*) Y. Hua and A. H. Flood, Click chemistry generates privileged CH hydrogen-bonding triazoles: the latest addition to anion supramolecular chemistry, *Chem. Soc. Rev.*, 2010, **39**, 1262–1271; (*d*) C. Le Droumaguet, C. Wang and Q. Wang, Fluorogenic click reaction, *Chem. Soc. Rev.*, 2010, **39**, 1233–1239; (*e*) J. M. Holub and K. Kirshenbaum, Tricks with clicks: modification of peptidomimetic oligomers via copper-catalyzed azide-alkyne [3+2] cycloaddition, *Chem. Soc. Rev.*, 2010, **39**, 1325–1337; For selected examples, see: (*f*) K. B. Sharpless and R. Manetsch, In situ click chemistry: a powerful means for lead discovery, *Expert Opin. Drug Discovery*, 2006, **1**, 525–538; (*g*) D. D. Diaz, K. Rajagopal, E. Strable, J. Schneider and M. G. Finn, "Click" Chemistry in a Supramolecular Environment: Stabilization of Organogels by Copper(ɪ)-Catalyzed Azide–Alkyne [3+2] Cycloaddition, *J. Am. Chem. Soc.*, 2006, **128**, 6056–6057; (*h*) J. F. Lutz, Copper-Free Azide–Alkyne Cycloadditions: New Insights and Perspectives, *Angew. Chem., Int. Ed.*, 2008, **47**, 2182–2184.

5 (*a*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, A Stepwise Huisgen Cycloaddition Process: Copper(ɪ)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599; (*b*) C. Tornoe, C. Christensen and M. Meldal, Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(ɪ)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides, *J. Org. Chem.*, 2002, **67**, 3057–3064.

6 (*a*) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini and M. J. Camarasa, 1,2,3-Triazole-[2,5-Bis-O-(tert-butyldi-

methylsilyl)-.beta.-D-ribofuranosyl]-3′-spiro-5″-(4″-amino-1″,2″-oxathiole 2″,2″-dioxide) (TSAO) Analogs: Synthesis and Anti-HIV-1 Activity, *J. Med. Chem.*, 1994, **37**, 4185–4194; (*b*) M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert and B. H. Yagi, Substituent Effects on the Antibacterial Activity of Nitrogen−Carbon-Linked (Azolylphenyl)oxazolidinones with Expanded Activity Against the Fastidious Gram-Negative Organisms *Haemophilus influenzae* and *Moraxella catarrhali*, *J. Med. Chem.*, 2000, **43**, 953–970.

7 For a review, see: (*a*) P. Saha, D. Panda and J. Dash, The application of click chemistry for targeting quadruplex nucleic acids, *Chem. Commun.*, 2019, **55**, 731–750; For selected examples, see: (*b*) D. Dutta, M. Debnath, D. Müller, R. Paul, T. Das, I. Bessi, H. Schwalbe and J. Dash, Cell penetrating thiazole peptides inhibit *c-MYC* expression via site-specific targeting of *c-MYC* G-quadruplex, *Nucleic Acids Res.*, 2018, **46**, 5355–5365; (*c*) R. Paul, D. Dutta, R. Paul and J. Dash, Target–Directed Azide–Alkyne Cycloaddition for Assembling HIV−1 TAR RNA Binding Ligands, *Angew. Chem.*, 2020, **59**, 12407–12411; (*d*) P. Saha, D. Panda, D. Müller, A. Maity, H. Schwalbe and J. Dash, *In situ* formation of transcriptional modulators using non-canonical DNA i-motifs, *Chem. Sci.*, 2020, **11**, 2058–2067.

8 (*a*) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, Copper-Catalyzed C−H Functionalization Reactions: Efficient Synthesis of Heterocycles, *Chem. Rev.*, 2015, **115**, 1622–1651 and the references therein; (*b*) R. Bohmann and C. Bolm, Copper-Catalyzed C–N Cross-Coupling of Sulfondiimines with Boronic Acids, *Org. Lett.*, 2013, **15**, 4277–4279; (*c*) Z.-B. Dong, X. Liu and C. Bolm, Copper-Catalyzed C(sp^2)–S Coupling Reactions for the Synthesis of Aryl Dithiocarbamates with Thiuram Disulfide Reagents, *Org. Lett.*, 2017, **19**, 5916–5919.

9 For reviews, see: (*a*) M. Meldal and C. W. Tornøe, Cu-Catalyzed Azide−Alkyne Cycloaddition, *Chem. Rev.*, 2008, **108**, 2952–3015; (*b*) J. E. Hein and V. V. Fokin, Copper-catalyzed azide–alkynecycloaddition (CuAAC) and beyond: new reactivity of copper(ɪ) acetylides, *Chem. Soc. Rev.*, 2010, **39**, 1302–1315; (*c*) V. K. Tiwari, B. B. Mishra, N. Mishra, K. B. Mishra, A. S. Singh and X. Chen, Cu-Catalyzed Click Reaction in Carbohydrate Chemistry, *Chem. Rev.*, 2016, **5**, 3086–3240; For selected examples, see: (*d*) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, Copper(ɪ)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates, *J. Am. Chem. Soc.*, 2005, **127**, 210–216; (*e*) V. O. Rodionov, S. I. Presolsky, S. Gardinier, Y.-H. Lim and M. G. Finn, Benzimidazole and Related Ligands for Cu-Catalyzed Azide–Alkyne Cycloaddition, *J. Am. Chem. Soc.*, 2007, **129**, 12696–12704; (*f*) C. Nolte, P. Mayer and B. F. Straub, Isolation of a Copper(ɪ)

Triazolide: A "Click" Intermediate, *Angew. Chem., Int. Ed.*, 2007, **46**, 2101–2103; (*g*) S. Őzçubukçu, E. Ozkal, C. Jimeno and M. A. Pericàs, A Highly Active Catalyst for Huisgen 1,3-Dipolar Cycloadditions Based on the Tris(triazolyl)methanol−Cu(ɪ) Structure, *Org. Lett.*, 2009, **11**, 4680–4683; (*h*) M. Liu and O. Reiser, A Copper(ɪ) Isonitrile Complex as a Heterogeneous Catalyst for Azide–Alkyne Cycloaddition in Water, *Org. Lett.*, 2011, **3**, 1102–1105; (*i*) S. Lal and S. Díez-González, [CuBr(PPh$_3$)$_3$] for Azide−Alkyne Cycloaddition Reactions under Strict Click Conditions, *J. Org. Chem.*, 2011, **76**, 2367–2373; (*j*) J.-A. Shin, J.-G. Lim and K.-H. Lee, Copper-Catalyzed Azide−Alkyne Cycloaddition Reaction in Water Using Cyclodextrin as a Phase Transfer Catalyst, *J. Org. Chem.*, 2012, **77**, 4117–4122; (*k*) R. Berg and B. F. Straub, Advancements in the mechanistic understanding of the copper-catalyzed azide–alkyne cycloaddition, *Beilstein J. Org. Chem.*, 2013, **9**, 2715–2750; (*l*) E. Tasca, G. L. Sorella, L. Sperni, G. Strukul and A. Scarso, Micellar promoted multi-component synthesis of 1,2,3-triazoles in water at room temperature, *Green Chem.*, 2015, **17**, 1414; (*m*) J.-A. Shin, S.-J. Oh, H.-Y. Lee and Y.-G. Lim, An efficient Cu-catalyzed azide–alkyne cycloaddition (CuAAC) reaction in aqueous medium with a zwitterionic ligand, betaine, *Catal. Sci. Technol.*, 2017, **7**, 2450–2456.

10 (*a*) Y. M. A. Yamada, S. M. Sarkar and Y. Uozumi, Self-Assembled Polymeric Copper Catalyst to Parts per Million Levels: Click Chemistry, *J. Am. Chem. Soc.*, 2012, **134**, 9285–9286; (*b*) W. Wang, F. Wei, Y. Ma, C.-H. Tung and Z. Xu, Copper(ɪ)-Catalyzed Three-Component Click/Alkynylation: One-Pot Synthesis of 5-Alkynyl-1,2,3-triazoles, *Org. Lett.*, 2016, **18**, 4158–4161; (*c*) B. G. Pasupuleti and G. Bez, CuI/*L*-proline catalyzed click reaction in glycerol for the synthesis of 1,2,3-triazoles, *Tetrahedron Lett.*, 2019, **60**, 142–146; (*d*) F. Krauskopf, K.-N. Truong, K. Rissanen and C. Bolm, [3+2]-Cycloadditions of N-Cyano Sulfoximines with 1,3-Dipoles, *Eur. J. Org. Chem.*, 2020, 2761–2765.

11 (*a*) W. G. Lewis, F. G. Magallon, V. V. Fokin and M. G. Finn, Discovery and Characterization of Catalysts for Azide–Alkyne Cycloaddition by Fluorescence Quenching, *J. Am. Chem. Soc.*, 2004, **126**, 9152–9153; (*b*) V. O. Rodionov, S. I. Presolski, S. Gardinier, Y. H. Lim and M. G. Finn, Benzimidazole and Related Ligands for Cu-Catalyzed Azide–Alkyne Cycloaddition, *J. Am. Chem. Soc.*, 2007, **129**, 12696–12704; (*c*) V. O. Rodionov, S. I. Presolski, D. D. Diaz, V. V. Fokin and M. G. Finn, Ligand-Accelerated Cu-Catalyzed Azide−Alkyne Cycloaddition: A Mechanistic Report, *J. Am. Chem. Soc.*, 2007, **129**, 12705–12712.

12 W. Wang, F. Hua, Y. Y. Jiang and Y. F. Zhao, Quick and highly efficient copper-catalyzed cycloaddition of aliphatic and aryl azides with terminal alkynes "on water", *Green Chem.*, 2008, **10**, 452–456.

13 (*a*) S. Díez-González and S. P. Nolan, [(NHC)$_2$Cu]X Complexes as Efficient Catalysts for Azide–Alkyne Click Chemistry at Low Catalyst Loadings, *Angew. Chem., Int. Ed.*, 2008, **47**, 8881–8884; (*b*) T. Nakamura, T. Terashima,

2440 | *Org. Chem. Front.*, 2021, **8**, 2434–2441

This journal is © the Partner Organisations 2021

K. Ogata and S. Fukuzawa, Copper(I) 1,2,3-Triazol-5-ylidene Complexes as Efficient Catalysts for Click Reactions of Azides with Alkynes, *Org. Lett.*, 2011, **13**, 620–623.

14 F. W. Li and T. S. A. Hor, Facile Synthesis of Nitrogen Tetradentate Ligands and Their Applications in Cu^I– Catalyzed N–Arylation and Azide–Alkyne Cycloaddition, *Chem. – Eur. J.*, 2009, **15**, 10585–10592.

15 (*a*) S. Paladhi, J. Das, M. Samanta and J. Dash, Asymmetric Aldol Reaction of Thiazole–Carbaldehydes: Regio– and Stereoselective Synthesis of Tubuvalin Analogues, *Adv. Synth. Catal.*, 2014, **356**, 3370–3376; (*b*) S. Paladhi, M. Bhati, D. Panda and J. Dash, Thiazolidinedione-Isatin Conjugates via an Uncatalyzed Diastereoselective Aldol Reaction on Water, *J. Org. Chem.*, 2014, **79**, 1473–1480; (*c*) G. Chakraborti, S. Paladhi, T. Mandal and J. Dash, "On Water" Promoted Ullmann-Type C–N Bond-Forming Reactions: Application to Carbazole Alkaloids by Selective N-Arylation of Aminophenols, *J. Org. Chem.*, 2018, **83**, 7347–7359.

16 As a chiral ligand is not necessary for this reaction, the reactions were carried out using D,L-proline and an achiral prolinamide **Pro-1** (prepared from D,L-proline) and the same results were obtained (Table S1, ESI†). However, chiral **Pro-1**, prepared from L-proline was used in this reaction as L-proline is easily available and commercially cheap compared to D,L-proline. .

17 (*a*) Y. P. Kumar, S. Bhowmik, R. N. Das, I. Bessi, S. Paladhi, R. Ghosh, H. Schwalbe and J. Dash, A Fluorescent Guanosine Dinucleoside as a Selective Switch–On Sensor for *c-myc* G–Quadruplex DNA with Potent Anticancer Activities, *Chem. – Eur. J.*, 2013, **19**, 11502–11506; (*b*) Y. P. Kumar, R. N. Das, S. Kumar, O. M. Schtte, C. Steinem and J. Dash, Triazole–Tailored Guanosine Dinucleosides as Biomimetic Ion Channels to Modulate Transmembrane Potential, *Chem. – Eur. J.*, 2014, **20**, 3023–3028.

18 (*a*) J. Andersen, U. Madsen, F. Björkling and X. Liang, Rapid Synthesis of Aryl Azides from Aryl Halides under Mild Conditions, *Synlett*, 2005, 2209–2213; (*b*) W. Zhua and D. Ma, Synthesis of aryl azides and vinyl azides via proline-promoted CuI-catalyzed coupling reactions, *Chem. Commun.*, 2004, 888–889.

19 B. T. Worell, J. A. Malik and V. V. Fokin, Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide-Alkyne Cycloadditions, *Science*, 2013, **340**, 457–460.

20 Y. C. Lin, Y. J. Chen, T. Y. Shih, Y. H. Chen, Y. C. Lai, M. Y. Chiang, G. C. Senadi, H. Y. Chen and H. Y. Chen, Mechanistic Study in Click Reactions by Using (*N*-Heterocyclic carbene)Copper(I) Complexes: Anionic Effects, *Organometallics*, 2019, **38**, 223–230.

21 H. B. El Ayouchia, L. Bahsis, H. Anane, L. R. Domingo and S. E. Stiriba, Understanding the mechanism and regioselectivity of the copper(I) catalyzed [3+2] cycloaddition reaction between azide and alkyne: a systematic DFT study, *RSC Adv.*, 2018, **8**, 7670–7678.

22 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman and D. J. Fox, *Gaussian 16, revision C.01*, Gaussian, Inc., Wallingford, CT, 2016.

23 Y. özkılıc and N. Ş. Tüzün, A DFT Study on the Binuclear CuAAC Reaction: Mechanism in Light of New Experiments, *Organometallics*, 2016, **35**, 2589–2599.

24 M. Ahlquist and V. Fokin, Enhanced Reactivity of Dinuclear Copper(I) Acetylides in Dipolar Cycloadditions, *Organometallics*, 2007, **26**, 4389–4391.

25 B. F. Straub, μ-Acetylide and μ-alkenylidene ligands in "click" triazole syntheses, *Chem. Commun.*, 2007, 3868–3870.

26 E. Boz and N. Ş. Tüzün, Ag-catalyzed azide alkyne cyclo-addition: a DFT approach, *Dalton Trans.*, 2016, **45**, 5752–5764.

27 (*a*) D. Maiti and S. L. Buchwald, Orthogonal Cu- and Pd-Based Catalyst Systems for the O- and N-Arylation of Aminophenols, *J. Am. Chem. Soc.*, 2009, **131**, 17423–17429; (*b*) D. Maiti and S. L. Buchwald, Cu-Catalyzed Arylation of Phenols: Synthesis of Sterically Hindered and Heteroaryl Diaryl Ethers, *J. Org. Chem.*, 2010, **75**, 1791–1794; (*c*) D. Maiti, Chemoselectivity in the Cu-catalyzed O-arylation of phenols and aliphatic alcohols, *Chem. Commun.*, 2011, **47**, 8340–8342.

28 (*a*) A. K. Ganai, P. Shinde, B. B. Dhar, S. S. Gupta and B. L. V. Prasad, Development of a multifunctional catalyst for a "relay" reaction, *RSC Adv.*, 2013, **3**, 2186–2191; (*b*) J. E. Camp, Auto–Tandem Catalysis: Activation of Multiple, Mechanistically Distinct Process by a Single Catalyst, *Eur. J. Org. Chem.*, 2017, 425–433; (*c*) Q.-J. Liang, Y.-H. Xu and T.-P. Loh, Multi-catalyst promoted asymmetric relay reactions, *Org. Chem. Front.*, 2018, **5**, 2765–2768; (*d*) H.-M. Huang, M. H. Garduño-Castro, C. Morrill and D. J. Procter, Catalytic cascade reactions by radical relay, *Chem. Soc. Rev.*, 2019, **48**, 4626–4638.

29 (*a*) L. F. Tietze and N. Rackelmann, Domino reactions in the synthesis of heterocyclic natural products and analogs, *Pure Appl. Chem.*, 2004, **76**, 1967–1983; (*b*) D. E. Fogg and E. N. dos Santos, Tandem catalysis: a taxonomy and illustrative review, *Coord. Chem. Rev.*, 2004, **248**, 2365–2379; (*c*) J. C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, Concurrent Tandem Catalysis, *Chem. Rev.*, 2005, **105**, 1001–1020.

This journal is © the Partner Organisations 2021

Org. Chem. Front., 2021, **8**, 2434-2441 | **2441**