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8-Hydroxyquinoline catalysed regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles: realizing Cu-free click chemistry

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Despite numerous reports on the Cu-catalysed click reaction and faster rates of reaction using such catalysts, the pharmacological application of this important synthetic method has become limited and hence advancement towards metal-free click chemistry has increasingly grabbed attention in recent years. Herein we report a regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles *via* a one-pot azide-alkyne cycloaddition reaction under metal-free conditions using the 8-hydroxyquinoline (8-HQ) catalyst. Along with a plethora of simple triazole derivatives, the protocol has been successfully applied to the synthesis of some bioactive compounds incorporating triazole motifs. Thorough control experiments including deuterium-labelling studies support the proposed mechanism for the reaction wherein the catalyst works as both a proton-abstractor and proton-donor synergistically.

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Introduction

The synthesis of 1,2,3-triazole motifs has been of paramount importance to chemists, owing to their profound pharmacological significance in antibacterial, anticancer,¹ antiviral,² and antituberculosis³ medications along with their widespread application in agrochemical industries as insecticidal⁴ and fungicidal agents.⁵ Huisgen pioneered the synthesis of triazoles in 1963 and laid the foundation of “1,3-dipolar cycloaddition reactions” to give rise to an array of five-membered heterocycles. Notably, under the broad umbrella of cycloaddition reactions, triazoles were the most pertinent scaffolds as a result of cycloaddition between azides and alkynes under thermal conditions.^{6,7} However, there were certain drawbacks associated with the classical Huisgen cycloaddition such as (i) slower reaction rates, (ii) high-temperature requirements and (iii) poor regioselectivity towards the 1,4 or 1,5 products. Subsequent efforts to overcome these drawbacks were conducted independently by the groups of Meldal⁸ and Sharpless⁹ who developed Cu-catalyzed azide alkyne cycloaddition (CuAAC) leading to the regiospecific formation of 1,4-disubstituted-1,2,3-triazoles under ambient conditions. Despite the widespread reports on Cu-based catalysts for the AAC reaction¹⁰ presenting enormously faster rates of reaction

(~10⁷ times faster compared to metal-free conditions),^{9,11} the difficulty in separating the copper particles from the final triazole products remained a problem, thereby limiting the scope of the conventional click chemistry for synthesizing medicinally viable triazole derivatives. Hence, the need for developing copper-free or other transition-metal-free catalytic systems for triazole synthesis has garnered increased attention among researchers in recent years.^{12,13} Bressy and co-workers revealed an atypical “amino-catalysis” route using the L-proline organocatalyst starting from unactivated ketones¹⁴ instead of alkynes *en route* to triazole synthesis unlike the groups of Ramachary^{12b} and Wang,¹³ who employed activated enones and ketones, respectively for such reaction. The observed high regioselectivity with the proline catalyst was substantiated by cycloaddition eventuating with the most stabilized enamine formed *in situ* by the reaction between the catalyst and the ketone. Fortuitously, the reaction could be performed under both thermal and microwave conditions while the latter expedited reaction rates.¹⁴

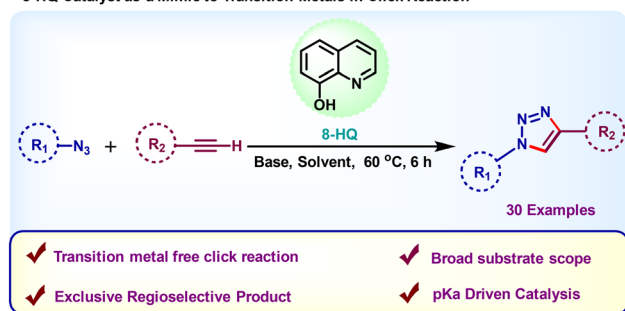
Apart from various transition metal-catalyzed reports on acetylenic anions acting as nucleophiles assisting cycloaddition with the azide partners, Lin and co-workers described the metal-free synthesis of 1,5-disubstituted-triazoles *via* the cycloaddition reaction. Accordingly, trimethylsilyl-substituted alkynes reacted with aromatic azides in the presence of an equivalent amount of potassium *tert*-butoxide as the desilylating agent to furnish the triazole product.¹⁵ Very recently, Ghatak's group has revealed the potency of “perimidin-2-imine”, which belongs to a class of *N*-heterocyclic imine (NHI) ligands, as a potent organocatalyst for regioselective 1,4-disubstituted triazole

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8-HQ Catalyst as a Mimic to Transition-Metals in Click Reaction



Scheme 1 General reaction scheme for the synthesis of 1,4-disubstituted-1,2,3-triazoles under metal-free conditions.

synthesis due to its $2\sigma,4\pi$ electron donor ability toward electron-deficient species.¹⁶ The same group had earlier reported a bimetallic Cu(II) catalyst coordinated to the same NHI ligand for the AAC reaction wherein one Cu atom binds to the acetylide and the other activates the azide in a synergistic manner leading to the quantitative preparation of numerous 1,4-disubstituted triazoles utilizing both aromatic and aliphatic alkyne partners under solvent-free conditions. Notably, their Cu(II) complex showed excellent activity towards the click reaction with TON values of about 120 000, which were unattainable with the previously reported Cu(II) catalysts.^{17a}

Furthermore, very recently, Tiwari and co-workers have described biocompatible silicomolybdic acid (SMA) catalysed synthesis of biologically relevant 4-aryl-NH-1,2,3-triazoles and glycosyl-NH-1,2,3-triazoles *via* a three-component reaction between aldehydes, nitroalkanes and sodium azide.^{17b} Notwithstanding the potential application of NHI as the first organocatalyst for the regioselective synthesis of 1,4-disubstituted triazoles through [3 + 2] cycloaddition between aryl azides and alkynes, its broad applicability is accompanied by certain drawbacks such as high cost and lengthy synthetic process for catalyst preparation and relatively longer reaction times. Therefore, to overcome the described challenges, there is a need to develop an efficient organocatalytic system of low cost and easy availability. Consequently, we were inspired to explore the utility of commercially available 8-hydroxyquinoline (8-HQ) as a catalyst for the streamlined synthesis of triazoles under metal-free and mild reaction conditions. We report herein the successful synthesis of a variety of 1,2,3-triazole derivatives in a regioselective 1,4-disubstituted fashion, mediated by the 8-HQ catalyst that operates under mild reaction reactions in the presence of a mild base, KO^tBu (Scheme 1).

Results and discussion

We began our preliminary investigation by choosing mesityl azide and phenylacetylene as the model substrates. We contemplated that a deprotonated form of 8-HQ will be the active catalyst therefore an equivalent amount of base was used for the reaction. DMSO was chosen as the reaction solvent owing to the pronounced acidity of aryl acetylenes in this solvent.¹⁸ We commenced our optimization reactions in

DMSO solvent using 5 mol% of 8-HQ catalyst along with 5 mol% KOH base at 100 °C for 24 h resulting in 30% yield of the regioselective 1,4-disubstituted triazole derivative (entry 3, Table S1). Doubling the catalyst and base loading to 10 mol% improved the product yield to 45% (entry 4, Table S1). To our delight, using a less nucleophilic base KO^tBu instead of KOH led to a two-fold increase in the product yield to 91% (entry 5, Table S1). Furthermore, a decrease in the reaction time and temperature to 6 h and 60 °C, respectively, did not seem to have any detrimental impact on the yield (entry 9, Table S1). A further decrease in the temperature afforded a significantly lower yield of the triazole product while the reaction was almost thwarted at room temperature. Solvent screening suggested toluene, THF and acetonitrile, under identical conditions, to afford merely 20–35% yields of the desired triazole derivative (entry 11, Table S1). Further attempts to check the viability of other N-donor systems instead of 8-HQ such as BIAN turned futile since it resulted in a negligible yield of the desired product (entry 12, Table S1). The critical role of the KO^tBu base was proved by the complete failure of the reaction in its absence (entry 2, Table S1). Finally, a blank reaction performed in the absence of the catalyst furnished merely 10% of the desired triazole product, proving the crucial role of the catalyst.

With the optimized reaction conditions in hand, we turned our attention to exploring the catalytic efficacy of the 8-HQ catalyst over a broad substrate range. Towards this goal, various aromatic azides with substituents like mesityl, 2,6-diisopropylphenyl, 2,6-dichloro phenyl and 4-*n*-butylphenyl were synthesized from the corresponding diazonium salts by reacting with sodium azide.¹⁹ Furthermore, to check the reactivity of aliphatic azides under our current catalytic protocol, benzyl azide derivatives were also synthesized by subjecting the corresponding benzyl chloride precursors to a simple nucleophilic substitution reaction with sodium azide at 0 °C in DMF solvent.²⁰ Likewise, a plethora of phenylacetylene derivatives bearing electron-donating and electron-withdrawing substituents at different positions of the phenyl ring were chosen as the alkyne partners for the AAC reaction.

Initially, mesityl azide was reacted with different phenyl acetylenes bearing alkyl groups at *ortho*-, *para*- and *meta*-positions of the phenyl ring to furnish the corresponding 1,4-triazole products in good yields (**4b–4d**). Notably, exclusive 1,4-regioselectivity of the products was ascertained by ¹H NMR spectroscopy without any formation of the 1,5-isomer.^{16,21} For instance, in the case of product **4a**, the appearance of a singlet peak for the C–H proton in the triazole ring at around δ 7.83 ppm unambiguously affirmed the exclusive formation of the 1,4-triazole product. In comparison, the 1,5-product exhibits a downfield signal at δ 8.00 ppm, that was missing in our reaction mixture. Next phenylacetylene bearing an electron-donating methoxy group at the *meta* position afforded 75% yield of the corresponding triazole product **4e**. Encouraged by these findings, we next subjected phenylacetylenes having electron-withdrawing



halide substituents like -F, -Cl, and -Br substituents to the current AAC reaction and obtained good yields (65–82%) of the corresponding products **4f–4h**. To our delight, the nitro group at the *para*-position of the phenylacetylene molecule was well-tolerated under the current reaction protocol albeit affording a moderate yield of **4i** (51%). Perhaps the highly electron-withdrawing -NO₂ group decreases the nucleophilicity of the acetylide anion considerably to affect the yield.¹⁶ An aromatic heterocyclic alkyne, 2-ethynyl pyridine, was also subjected to the current reaction protocol, yielding 87% of the target triazole product **4j** (Table 1).

By the same token, we next treated 2-azido-1,3-diisopropylbenzene with a variety of substituted phenylacetylenes affording good to excellent yields of corresponding triazole products **5a–5h**. Notably, a pyridine ring was successfully installed in the triazole ring as was apparent by the formation of **5h** (80%). Apart from products **6a–6f**, obtained by the cycloaddition reaction utilizing simple phenyl azide, substituted phenyl azides such as 2,6-dichlorophenyl azide and 4-*n*-butylphenyl azide were also successful in synthesizing the triazole products **7a** and **8a** in 89% and 71% yields, respectively.

Table 1 Substrate scope for phenyl azide & phenylacetylene derivatives; reaction conditions: phenyl azide (0.5 mmol), substituted phenylacetylene (0.5 mmol), KO^tBu (10 mol%), **1** (10 mol%), DMSO (2 mL), 60 °C, 6–16 h

2a - 2g (0.5 mmol) 3 (0.5 mmol) 4a - 4j, 5a - 5h, 6a - 6f, 7a, 8a, 9a - 9g					
Cat. 1					
4a (68%); gram scale (59%)	4b (71%)	4c (79%)	4d (72%)	4e (75%)	4f (65%)
4g (78%)	4h (82%)	4i (51%)	4j (87%)	5a (78%)	5b (88%)
5c (86%)	5d (93%)	5e (79%)	5f (71%)	5g (79%)	5h (80%)
6a (76%)	6b (92%)	6c (88%)	6d (67%)	6e (91%)	6f (87%)
6g (n.r.)	6h (n.r.)	6i (n.r.)	6j (n.r.)	6k (n.r.)	6l (n.r.)
7a (89%)	8a (71%)	9a (62%); gram-scale (54%)	9b (67%)	9c (46%)	
9d (n.r.)	9e (n.r.)	9f (n.r.)	10a (65%)		



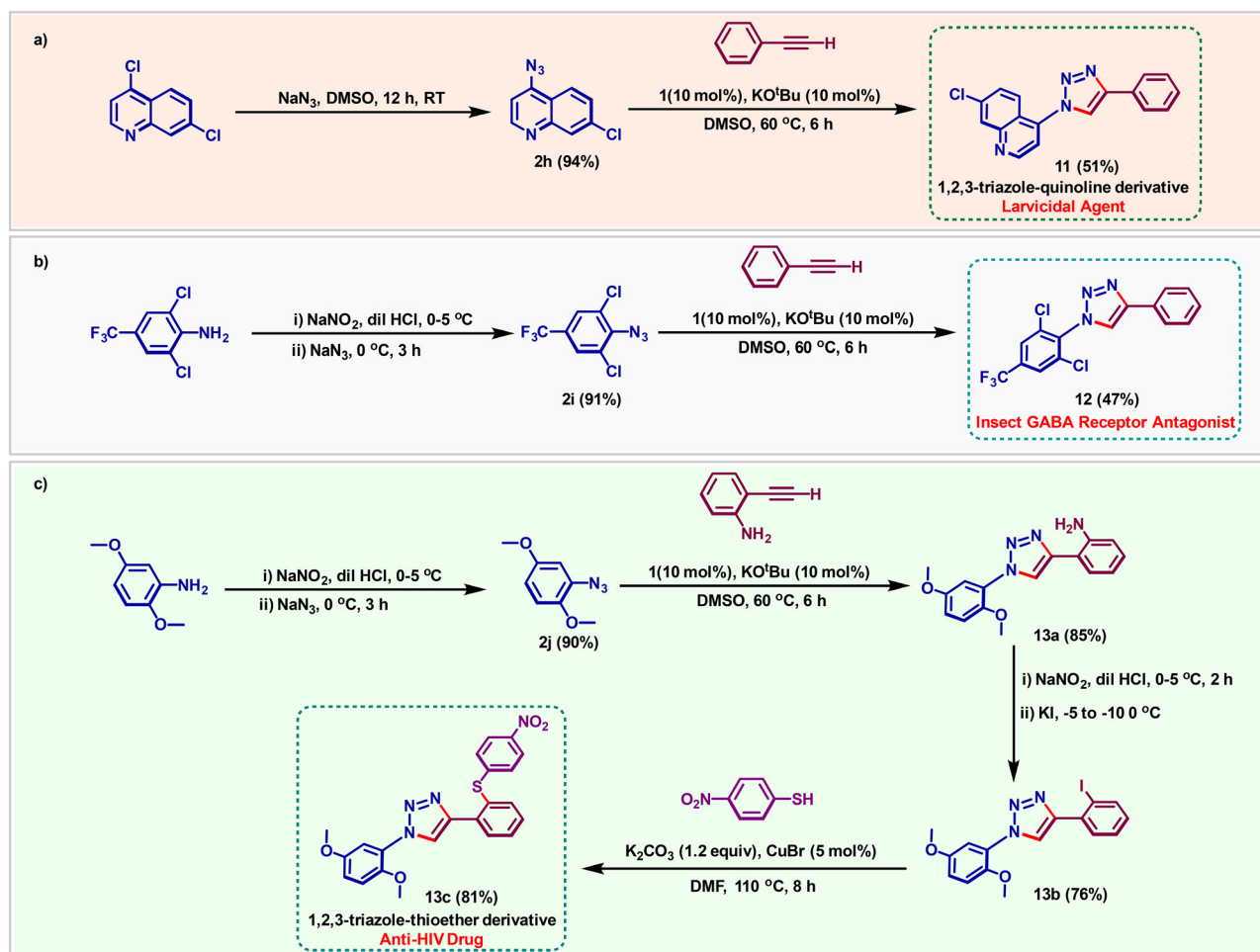
Diversification towards synthesis of bioactive triazoles

Inspired by these findings, we explored the scope of the catalyst with more challenging aliphatic azides. For this purpose, benzyl azide and 4-methylbenzyl azide were chosen as the azide partners forming the targeted triazole products successfully (**9a–9c** and **10**). A gram-scale reaction was performed using benzyl azide and phenylacetylene, which afforded nearly 54% yield of the corresponding triazole derivative **9a**. The formation of triazole **9c** was encouraging since it involved the cycloaddition reaction between the highly challenging aliphatic azide and phenylacetylene derivative. Unfortunately, few more challenging aliphatic alkynes were reacted with aryl azides such as phenyl azide and mesityl azides but they failed to afford the desired triazole derivatives (**6g–6l**). Similarly, benzyl azide also failed to give the targeted triazole compounds **9d–9f** upon reaction with the corresponding aliphatic alkynes. This might be due to less acidity of the acetylenic proton in aliphatic alkynes, which makes the deprotonation step highly challenging. Given wide pharmacological significance of many triazole motifs, we were keen on applying this metal-free reaction protocol toward the

synthesis of a few bioactive compounds comprising the triazole ring (Scheme 2). In this direction, we performed a mono-azidation reaction using 4,7-dichloroquinoline resulting in the formation of 4-azido-7-chloroquinoline **2h**. This was subjected to the current cycloaddition reaction using phenylacetylene as the reaction partner finally affording 1,2,3-triazolequinoline hybrid **11** in 51% yield. Notably, compound **11** and similar 7-chloro-4-(1*H*-1,2,3-triazol-1-yl)quinoline derivatives have been reported to exhibit larvicidal properties.^{4b} Furthermore, product **12**, 1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-phenyl-1*H*-1,2,3-triazole was synthesized that was earlier proved as an insect GABA receptor antagonist.^{4a} By the same token, 2-(1-(2,5-dimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)aniline, *i.e.* compound **13a**, synthesized by the AAC reaction between 2-azido-1,4-dimethoxybenzene and 2-ethynyl aniline was post-functionalized sequentially to finally afford product **13c** in 81% yield. Notably, this triazolethioether derivative is an anti-HIV drug by acting as a viral infectivity factor (Vif) antagonist.²

Control experiments

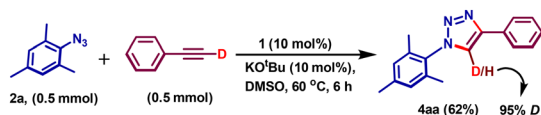
A series of control experiments were performed to elucidate the possible mechanism for the catalytic reaction. First, to



Scheme 2 (a–c) Diversification towards the synthesis of bioactive triazole derivatives.

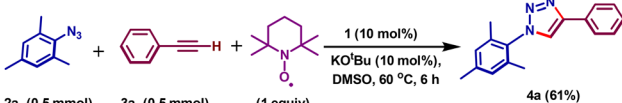


a) Deuterium labeling experiments:

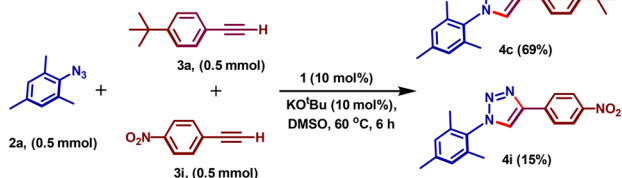


b) Radical trapping experiments:

1. Radical trapping experiment for mesityl azide:



c) Competitive AAC reactions:



Scheme 3 Control experiments for the mechanistic investigation.

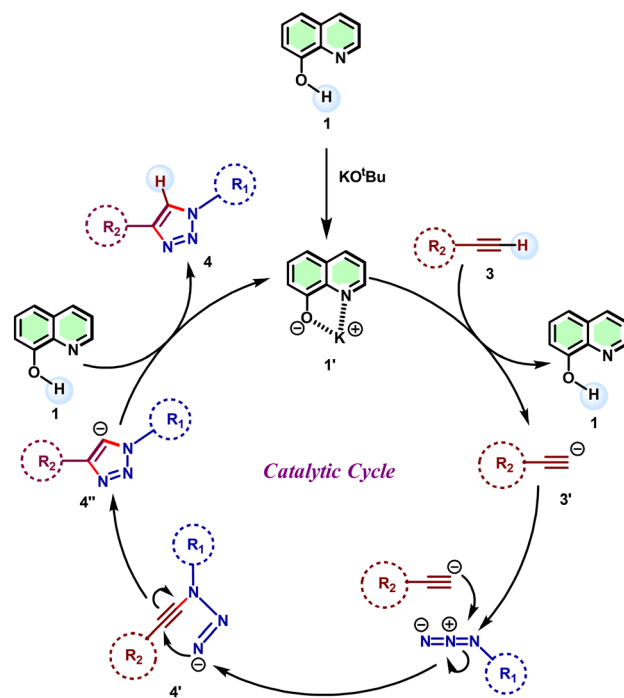
confirm the source of the proton in the triazole ring is phenylacetylene, a catalytic reaction was performed between mesityl azide and deuterated phenylacetylene. The *d*-labelled phenylacetylene used for this reaction had 96% *d*-incorporation using a reported method.²² In the AAC reaction starting with deuterated phenylacetylene, we found 95% *d*-incorporation. This experiment unambiguously confirmed that the sole source of C–H proton in the triazole ring of **4aa** is phenylacetylene (Scheme 3a). Next, a reaction performed in DMSO-*d*₆ under optimal conditions did not lead to any *d*-incorporation in the triazole ring. This observation refuted the possibility of final protonation by DMSO solvent as proposed by Fokin (Section 5b, SI).²¹ To check the possibility of kinetic isotope effect (KIE), we performed a competitive reaction between mesityl azide and both equimolar quantities of both phenylacetylene and phenylacetylene-*d* in a single pot. Upon careful examination of the purified triazole product **4a** by ¹H NMR, the KIE or *k*_H/*k*_D value was found to be 2.57, clearly proving that the reaction exhibits a kinetic isotope effect (SI, Section 5e).

To substantiate that the potassium adduct of 8-HQ is the active catalyst generated *in situ*, we tried to isolate the actual form of the latter. As an initial clue, we observed the yellow color of 8-HQ in DMSO solution to intensify upon the addition of KO^tBu. However, several attempts to isolate crystals of **1'** in the presence of 18-C-6 in DMSO remained elusive. The involvement of radical intermediates during the reaction course was refuted as radical quenchers such as TEMPO and BHT did not have any detrimental effect on the reaction (Scheme 3b). To understand the influence of electron-donating and electron-withdrawing groups at the alkyne side on the reaction, a competitive reaction was performed wherein 0.5 mmol of mesityl azide was reacted with equimolar quantities of 4-*tert*-butylphenylacetylene and 4-nitrophenylacetylene in the same reaction flask and corresponding triazole products **4c** and **4i** were purified

through column chromatography. Consequently, the isolated yield of **4c** and **4i** was found to be 69% and 15% respectively, which demonstrated that the electron-withdrawing group on the phenylacetylene lowered the nucleophilicity of the acetylide species thereby retarding the product formation (Scheme 3c).¹⁶

Reaction mechanism

In light of the control experiments and previous literature reports,^{16,21,24} a plausible mechanistic cycle for the formation of 1,4-disubstituted 1,2,3-triazoles from aryl azides and phenylacetylene has been proposed in Scheme 4. The first step involves the deprotonation of 8-HQ by the KO^tBu base, analogous to the deprotonation of BTAN molecule by the same base as has been previously established in the literature,²³ leading to the generation of the potassium complex of 8-HQ, **1'**, which acts as an active catalyst. Also, this deprotonation step is congruent with the reported *pK*_a values being 17 and 9.9 for KO^tBu and 8-HQ respectively. Hence the base is likely to deprotonate the 8-HQ pre-catalyst in the first step instead of phenylacetylene (*pK*_a = 20.1). This is followed by the reversible deprotonation of phenylacetylene by the active catalyst thereby generating phenyl acetylide species **3'**. It can be hypothesized that the deprotonation of phenylacetylene is reversible since the generated acetylide species **3'** can revert back to **3** by abstracting a proton from adventitious moisture or *tert*-butanol. However in the presence of an azide partner, the reaction essentially proceeds towards the 1,3-dipolar addition of **3'** and azide



Scheme 4 Plausible mechanism for the click reaction by the 8-HQ catalyst.



resulting in the formation of intermediate **4'**, which further undergoes cyclization to give the triazolide species **4''**. In the final step, the triazolide **4''** deprotonates the –OH group of the catalyst thereby transferring the proton to the triazolide and regenerating the active catalyst **1**.

Conclusion

To summarize, 8-HQ has been employed as an efficient catalyst for the 1,3-dipolar cycloaddition reaction between azide and alkyne. The method works well for a wide variety of aromatic azides such as substituted phenyl azides as well as for aliphatic azides such as benzyl azide derivatives to yield the corresponding triazole derivatives. Besides, the synthetic method has been utilized for the successful synthesis of a few bioactive compounds. Various control experiments substantiate the crucial role of the 8-HQ catalyst functioning as both a proton-abstractor and proton-donor throughout the catalytic cycle. In effect, click chemistry under metal-free conditions in general, or Cu-free conditions to be specific, renders the overall triazole synthesis process sustainable and economically viable, which promises to find use in pharmacological applications.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There is no conflict of interest to declare.

Data availability

Supplementary information available: Detailed synthetic procedure, control experiments, characterization details, NMR spectra. See DOI: <https://doi.org/10.1039/D5CY00598A>.

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