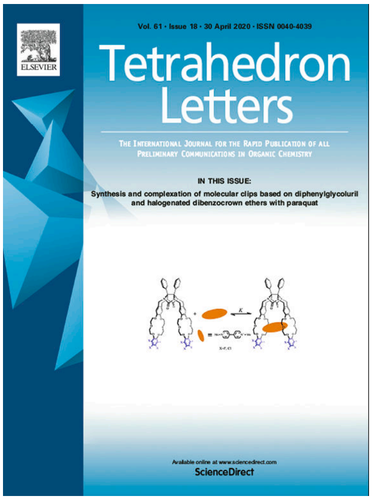

# A bile acid-based pyridino-triazole ligand for Cu(I)-stabilization and its application in Cu(I) catalyzed click reactions

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# A bile acid-based pyridino-triazole ligand for Cu(I)-stabilization and its application in Cu(I) catalyzed click reactions

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Keywords: Bile acid, Triazole, Click reaction.

## Abstract

A bile acid based pyridino-triazole ligand to stabilize Cu(I) state has been developed. The ligand was found to catalyze click reactions of a number of alkynes and azides in presence of $Cu(CH_3CN)_4.BF_4$ at very low catalyst loading and under milder reaction conditions.

## Introduction

The Cu(I)-catalyzed cycloaddition reaction between an azide and an alkyne yielding 1,4-disubstituted 1,2,3-triazoles developed independently by Meldal [1] and Sharpless [2] has found its extensive applications in a wide range of fields such as polymer chemistry, materials science, medicinal chemistry and supramolecular chemistry [3]. Due to its importance in the field of chemistry and related sciences, there has been considerable effort to design ligands for the stabilization of Cu(I) state [4]. The presence of ligands is not only crucial for the protection of the Cu(I) species from oxidation and disproportionation but is also responsible for the facilitation and acceleration of the overall cycloaddition reactions in milder reaction conditions.

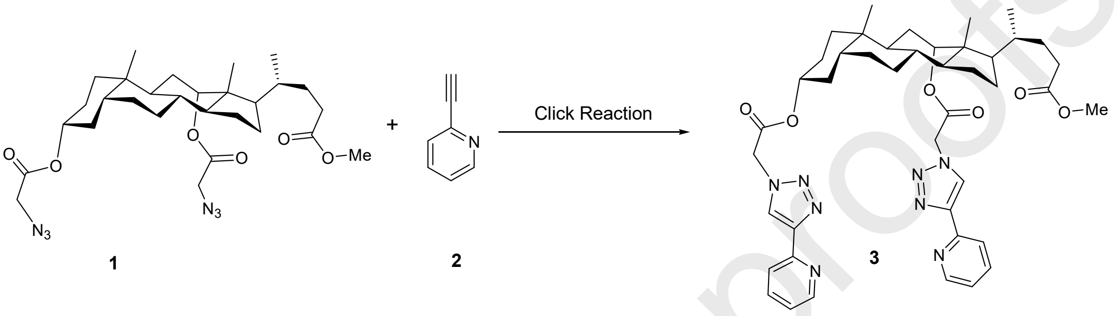
A range of click polydentate ligands have been reported and their coordination and catalytic properties with a variety of metal ions are examined [5-7]. Fokin and co-workers synthesized tris(benzyltriazolylmethyl)amine (TBTA) using Cu(I)-catalyzed click reaction. They discovered that TBTA acts as a stabilizing ligand for Cu(I), which protect it from oxidation and disproportionation and acts as a powerful catalyst for click reaction [8]. Williams and co-workers prepared and characterized two Cu(II) and Cu(I) complexes of tris(benzyltriazolylmethyl)amine (TBTA) ligand and studied their application in cycloaddition reaction between phenylacetylene and azidoacetanilide [9]. A neutral, air and moisture stable Cu(I) complex bearing a tris(benzyltriazolyl)methanol ligand was reported by Pericàs and co-workers for CuAAC reactions in water or under neat conditions [10]. Prez and co-workers immobilized tris-(benzyltriazolylmethyl)amine (TBTA) to a styrenic monomer and subsequently copolymerized with styrene to afford catalytically active and reusable copolymers for the CuAAC reaction [11]. Pericás and co-workers synthesized a polystyrene resin supported Cu(I) complex, which acted as catalyst in both aqueous and organic media [12]. L-Valine-derived low-molecular-weight gelators functionalized with triazole units were synthesized by Escuder and co-workers. The gelator-coordinated Cu(I), building hybrid organic–inorganic gels, were utilized in catalyzing the cycloaddition of alkynes and azides [13]. Astruc and co-workers synthesized an amphiphilic ligand tris(triazolyl)polyethylene glycol (tris-trz-PEG) and used it for synthesis of Cu nanoparticles as a catalyst for CuAAC reaction between benzyl azide and phenylacetylene [14]. Cai and co-workers synthesized a library of Cu(I) tripodal triazolyl ligands varying in chelate arm length and evaluated their structural effects on the CuAAC reaction, air oxidation, and ligand dissociation [15].

Bile acids, natural compounds of the steroid family, with slightly curved shape backbone possessing carboxy and hydroxyl groups of varied reactivity, have been very attractive as building blocks for the design of molecular and ionic receptors [16]. Their special characteristics offer a unique spatial structural arrangement for building receptors with different sized cavities and varied binding sites. Bile acid derivatives with 1,2,3-triazole units have received special attention in ionic recognition because of their unique geometry and coordination properties with anions and metal ions [17]. To explore the role of the inherent features of bile acid framework in generating polydentate Cu(I)-stabilizing ligands, we have designed and synthesized a steroidal tetradentate pyridino-triazole ligand and examined its catalytic potential for the Cu(I)-catalyzed click reaction. Our experimental results suggest that this system is capable of stabilizing Cu(I) state in organic solvents, which leads to low catalyst loading and excellent catalytic activity for a wide range of substrates.

## Results and Discussion

### Synthesis of ligand

The bile acid based triazole ligands **3** was synthesized by the treatment of methyl 3α,12α-bis-(azidoacetyl)deoxycholate **1** [17a] with 2-ethynylpyridine (**2**), in the presence of $CuSO_4$ (10 mol %) and sodium ascorbate (20 mol %) in *t*-BuOH / $H_2O$ at 60 °C (Scheme 1).



**Scheme 1**: Synthesis of bile acid-based pyridine-triazole ligand **3**

### Binding behaviour of 3 towards Cu(I) salt

The binding behaviour of ligand **3** towards Cu(I) salt $\{Cu(CH_3CN)_4.BF_4\}$was studied through UV-Vis titration. A clear spectral change upon the addition of aliquots of Cu(I) solution to the solution of the compound **3** in DCM was observed (Fig 1). A gradual increase in absorbance between 320 nm and 400 nm with appearance of a new band at 360 nm was observed with the increasing concentration of Cu(I) due to the formation of a metal-ligand charge transfer (MLCT) complex between ligand and Cu(I) (Fig. 2). A similar situation was reported earlier for a pyridino-triazole ligand with complexation with Cu(I) [18]. The Job's plot analysis exhibited 1:1 complexation between Cu(I) and ligand 3 (Fig. S3).

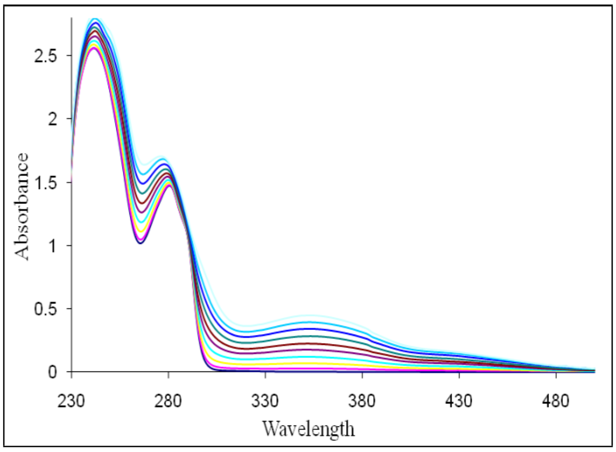


**Figure 1**: Absorption spectra of **3** ($3 \times 10^{-5}$ M) upon titration with $Cu(CH_3CN)_4.BF_4$ (0−2.6 equiv) in $CH_2Cl_2$

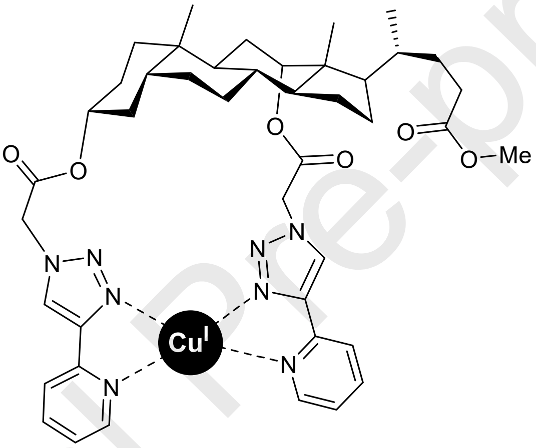
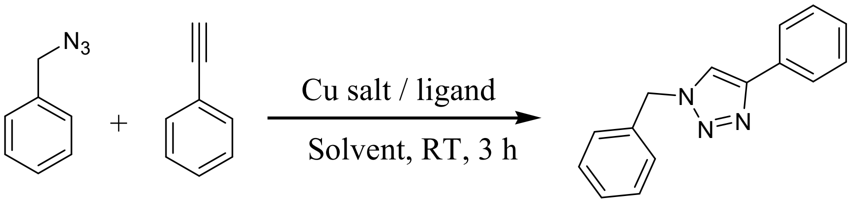


**Figure 2**: Proposed binding model

**Click reactions catalyzed in presence of ligand 3 and Cu(I) salts**

The catalytic activity of Ligand **3** was examined for click reactions of various azides and terminal alkynes in presence of Cu(I) salts. For carrying out primary investigations on catalytic activity of **3** for the click reaction, benzyl azide was reacted with phenyl acetylene in DCM in the presence of ligand **3** and $[Cu(CH_3CN)_4].BF_4$ (1 mol %) (Scheme 2).



**Scheme 2**: Cu(I)-catalyzed click reaction in presence of **3**

The reaction proceeded smoothly in the presence of **3** (1 mol %). After carrying out reaction for 3 h at room temprature, the product was obtained in 100 % yield (Table 1; Entry 1). In the absence of **3**, the product yield was found to be only 4% under similar reaction conditions (Table 1; Entry 2). On replacing DCM with solvents THF, acetonitrile, aqueous *t*-butanol, ethanol and acetone, yield was significantly reduced (Table 1; Entries 3-8). For the optimization process, various Cu(I) salts such as CuI, CuBr, CuCl, and $Cu_2O$ have been used for the model reaction in presence of **3** (Table 1; Entries 9-12). However, the best result was obtained when $[Cu(CH_3CN)_4]BF_4$ was used as Cu(I) salt and DCM was used as solvent (Table 1; Entry 1).

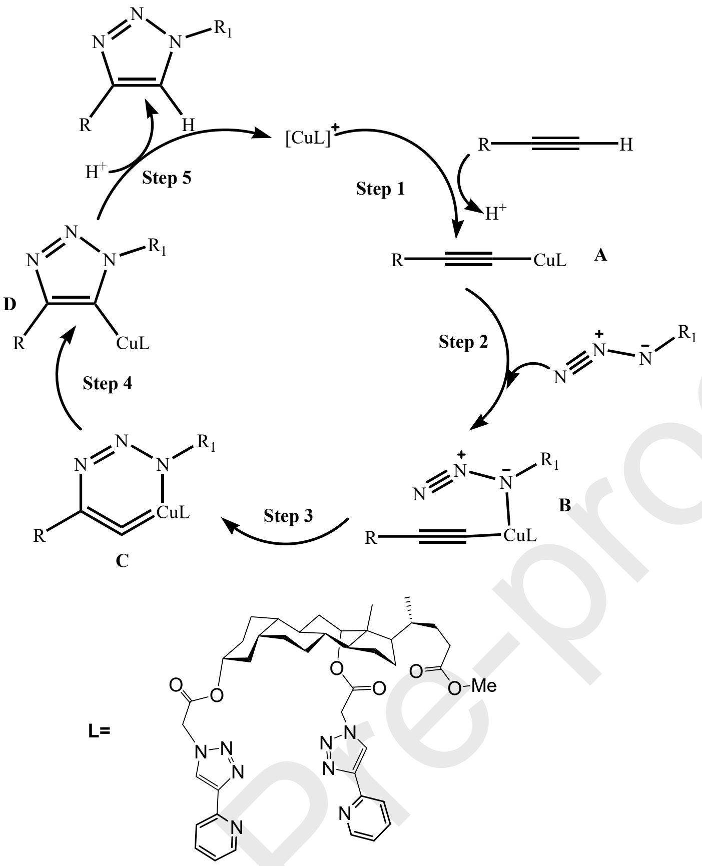
**Table 1. Standardization of reaction conditions**[a]

| Entry | Cu (I) Source | Ligand | Solvent | NMR Yield[b] (%) |
|---|---|---|---|---|
| 1. | $Cu(CH_3CN)_4.BF_4$ | **3** | DCM | 100 (96) |
| 2. | $Cu(CH_3CN)_4.BF_4$ | **-** | DCM | 4 |
| 3. | $Cu(CH_3CN)_4.BF_4$ | **3** | THF | 40 |
| 4. | $Cu(CH_3CN)_4.BF_4$ | **3** | *t*-BuOH-$H_2O$ | 75 |
| 5. | $Cu(CH_3CN)_4.BF_4$ | **3** | $CH_3CN$ | 36 |
| 6. | $Cu(CH_3CN)_4.BF_4$ | **3** | $C_2H_5OH$ | 63 |
| 7. | $Cu(CH_3CN)_4.BF_4$ | **3** | $CH_3COCH_3$ | 42 |
| 8. | $Cu(CH_3CN)_4.BF_4$ | **3** | No Solvent | 95 (89) |
| 9. | $Cu_2O$ | **3** | DCM | trace |
| 10. | CuI | **3** | DCM | 27 |
| 11. | CuBr | **3** | DCM | 0 |
| 12. | CuCl | **3** | DCM | 56 |

[a] Reaction conditions: 1.0 mmol benzyl azide, 1.1 mmol phenyl acetylene, RT, Reaction time 3 h, Cu(I) salt (1 mol %), Solvent 5 mL, **3** (1 mol %). [b] In parentheses are shown the isolated yields after column chromatography.

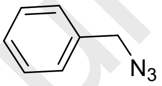
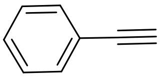
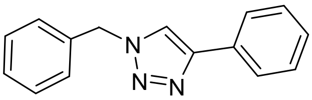
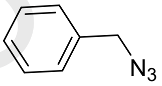
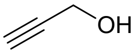
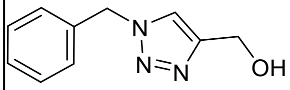
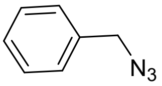
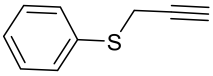
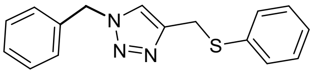
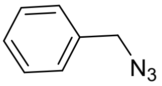
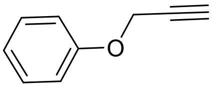
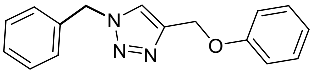
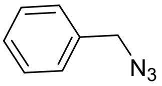
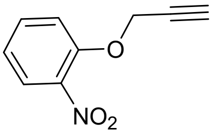
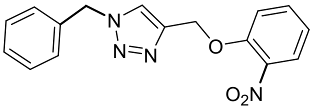
The click reaction of benzyl azide with phenyl acetylene also proceeded smoothly when no solvent was used (neat reaction) and the product was obtained in 95% yield. Subsequently, click reactions of a variety of terminal alkynes including aliphatic and aromatic systems were carried out using **3** as a catalyst. The results are presented in Table 2.

The 1,4-disubstituted 1,3-cycloaddition products are formed following the reaction mechanism proposed by Fokin and co-workers [6] (Scheme 3).



Scheme 3: Mechanism for Cu(I)-catalyzed azide–alkyne cycloaddition reaction using bile acid-based pyridine triazole ligand

**Table 2 Click reactions catalyzed in presence of ligand 3[a]**

| Entry | Azide | Alkyne | t (h) | Product | Yield[b] |
|---|---|---|---|---|---|
| 1 |  |  | 3 |  (4a) | 96 |
| 2 |  |  | 10 |  (4b) | 92 |
| 3[d,e] |  |  | 12 |  (4c) | 83 |
| 4[d,e] |  |  | 12 |  (4d) | 94 |
| 5[d,e] |  |  | 12 |  (4e) | 83 |

| | | | | | |
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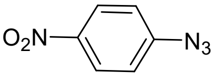
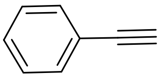
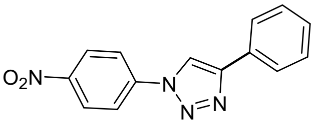
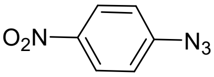
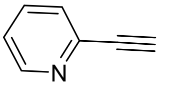
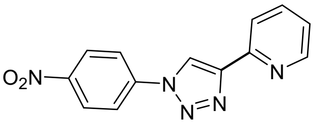
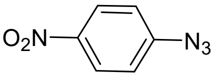
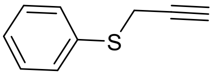
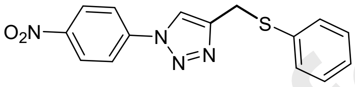
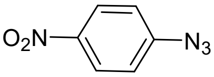
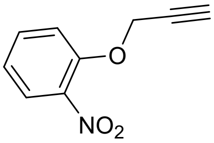
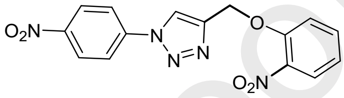
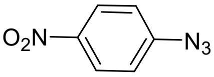
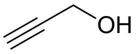
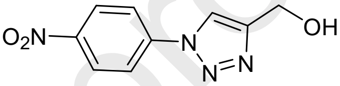
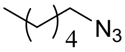
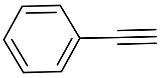
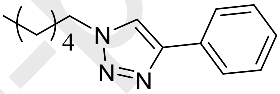
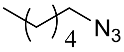
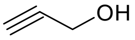
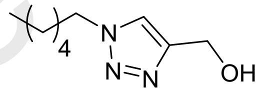
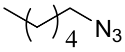
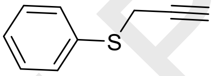
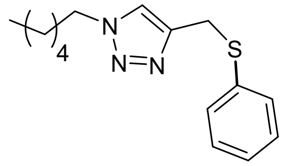
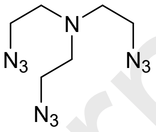
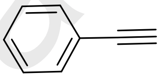
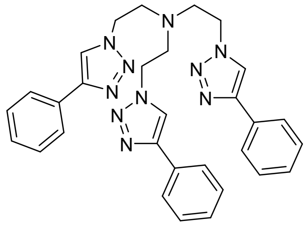
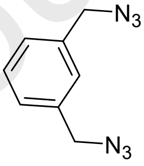
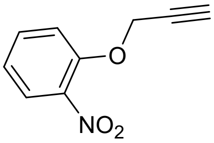
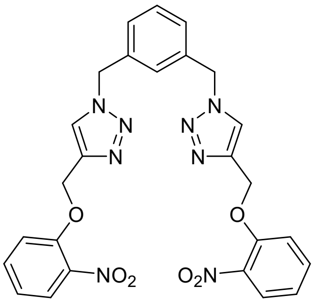
| 6[c] |  |  | 6 |  (4f) | 91 |
| 7[c] |  |  | 8 |  (4g) | 86 |
| 8[c] |  |  | 3 |  (4h) | 89 |
| 9[c] |  |  | 8 |  (4i) | 93 |
| 10[c] |  |  | 3 |  (4j) | 89 |
| 11 |  |  | 3 |  (4k) | 90 |
| 12 |  |  | 15 |  (4l) | 88 |
| 13[d] |  |  | 15 |  (4m) | 84 |
| 14[c,f] |  |  | 6 |  (4n) | 86 |
| 15[d,e,g] |  |  | 10 |  (4o) | 92 |

[a] Reaction conditions: 1.0 mmol benzyl azide, 1.1 mmol phenyl acetylene, RT, DCM 5 mL, Cu(I) salt (1 mol %), **3** (1 mol %). [b] Isolated yield after column chromatography. [c] Column not required. [d] Reaction temperature was 40 °C. [e] Cu(I) salt (2 mol%) and **3** (2 mol %). [f] 4 mmol of alkyne was used. [g] 2.0 mmol of alkyne was used.

All reactions proceeded smoothly to completion in 3–15 h and triazoles were isolated in excellent yields in high purity by simple filtration through short silica column. Benzylic, alkyl and aryl azides all reacted very well in the presence of **3**. Electron-rich, electron-poor and / or hindered alkynes all gave good yields. However, alkynes with adjacent heteroatoms (O, S) seem to require longer reaction time (10−15 h) and slightly higher temperature (Entries 2−5, 13 and 15). When 4-nitrobenzene azide was reacted with various alkynes, the corresponding click products precipitated out due to their lower solubility in DCM and could be easily separated by filtration (Entries 6−10 and 14). No column chromatography was required in such cases.

## Conclusion

We have designed and synthesized a bile acid based 1,2,3-triazole ligand containing pyridine moiety for stabilization of Cu(I) ion. This ligand has been found to show excellent catalytic activity for cycloaddition reactions of a number of alkynes and azides in the presence of $Cu(CH_3CN)_4.BF_4$. Very low catalyst loading (1 mol % of Cu(I) and 1 mol % of ligand) and milder reaction conditions are required for the click reaction of a wide range of substrates. Reactions are very clean and, in many cases, column chromatography in not required.

## Acknowledgement

AN thanks the Council of Scientific and Industrial Research, New Delhi, for the research fellowship.

## Supplementary data

The experimental procedure for the synthesis of the ligand and click products, and their $^1H$ and $^{13}C$ NMR spectra are available in supporting information.

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## Declaration of Interest statement

10-07-2020

Professor Vinod Singh

Associate Editor

Tetrahedron Letters

Subject: Declaration of Interest statement

Dear Professor Singh,

Please find the manuscript entitled "**A bile acid-based pyridino-triazole ligand for Cu(I)-stabilization and its application in Cu(I) catalyzed click reactions**" for publication in Tetrahedron Letters.

The article demonstrates the synthesis and catalytic properties of a bile acid-based tetradentate pyridino-triazole ligand for the Cu(I)-catalyzed click reaction. The ligand was found to catalyze click reactions of a number of alkynes and azides in presence of $Cu(CH_3CN)_4.BF_4$ at very low catalyst loading and under milder reaction conditions. Over past years, there has been considerable interest on design of ligands and their application in copper catalyzed azide–alkyne cycloaddition (CuAAC) reactions. Hence, the steroidal tetradentate pyridino-triazole ligand, being reported for the first time, will be of a particular interest as an efficient catalyst for the CuAAC reactions.

The work presented in the manuscript have not been submitted or published in any other journal. We hope that the manuscript would be reviewed and considered for publication in Tetrahedron Letters.

Best regards,

Yours Sincerely,
Pramod S Pandey
Former Professor
Department of Chemistry
Indian Institute of Technology Delhi
New Delhi 110016
India

**Highlights**

- Synthesis of a pyridino-triazole ligand based on bile acid framework.
- The bile acid-based pyridino-triazole ligand stabilizes Cu(I) state.
- The ligand catalyzes click reactions in presence of $Cu(CH_3CN)_4.BF_4$.