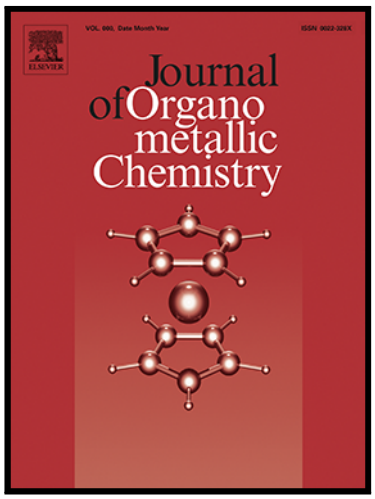

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Highlights:

1) Here we synthesized pyrazole based tridentate ligand and its copper(II) catalyst in simple route.
2) We have also studied the efficiency of the catalyst for the azide-alkyne cycloaddition and azide reduction reactions.
3) The ligand as well as the catalyst were well studied with spectroscopic techniques and single crystal XRD.

Synthesis of new Copper Catalyst with Pyrazole Based Tridentate Ligand and Study of Its Activity for Azide Alkyne Coupling

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Keywords: Tridentate ligand, copper catalyst, Click reaction, azide reduction, pyrazole

1. Introduction

Transition metal complexes have emerged as one of the important members of catalyst for organic reactions in the last few decades [1]. More specifically, copper complexes have received more attention due to their redox behaviour, ability to form stable complex readily with several ligands, easy accessibility and economic reasons [2]. Copper(II) is also an essential trace element in all living system which has so many important biological role like oxygen transport and redox reactions [3]. In the recent past, several research groups have studied the anticancer activity of Copper(II) complexes which contain derivatives of sevevral heterocycles [4]. They have also been studied for biological activities such as cytotoxicity against cancer cells, anticancer activity, antiviral activity and DNA and protein cleavage activity [5]. In particular, copper(II) complexes containing pyrazole derivative show antitumor activity similar to that of cisplatin [6]. Also, this pyrazole moiety in copper(II) complexes has some promising pharmacological, agrochemical and analytical applications [7].

Copper complexes are widely used in the organic transformation including asymmetric synthesis, [3+2] cycloaddition between azide and alkyne, popularly known as click reaction [8], cyclopropanation of diazo compounds *via* carbenoid [9], aldol-type reaction, Mannich reaction [10], Diels-Alder reaction [11] are a few to be highlighted. The

most common types of ligands for copper include bisoxazoline, Phenanthroline, salen, imine and amine based ligands (**Fig.1**)

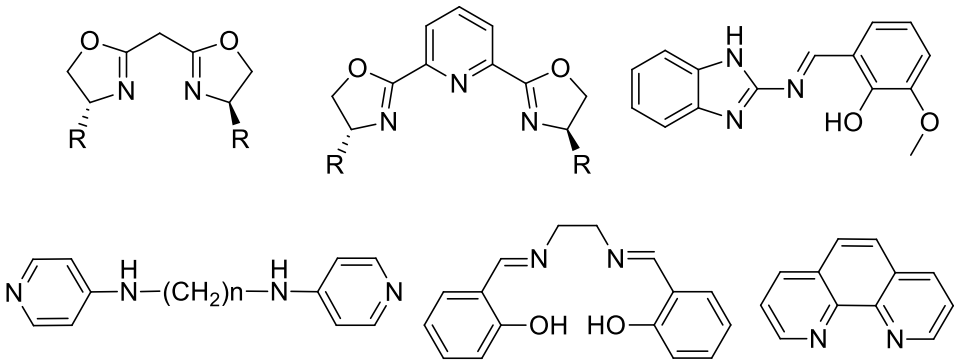


Fig.1: Common types of ligands for Copper

The copper(II)-catalysed Huisgen [3+2] dipolar Cycloaddition (CuAAC) [12] between terminal alkynes and organic azide has arguably become the most popular ligation reaction to give 1,4-disubstituted 1,2,3-triazoles and exhibits remarkably broad scope and exquisite selectivity. Thus obtained 1,2,3-triazole derivatives have been utilized as dyes, photo stabilizers, agrochemicals, and biochemical polymer, drug discovery, advanced material science, etc [13]. More attention has been paid to the development of copper(I) catalytic systems for CuAAC reactions, a direct method for the preparation of a extensive range of five-membered ring heterocycles [14]. Most of the described catalytic system generate Cu(I) *via in situ* reduction of Cu(II) by sodium ascorbate, oxidation of Cu(0) to Cu(I) *via* oxidation or Cu(II)/Cu(I) comproportionation reactions. Copper(I) salts are least used because of their common thermodynamic instablility [15], except copper(I) iodide.

2. Experimental Section

2.1. Synthesis of 3,5-dimethyl-1-(2-nitrophenyl)-1H-pyrazole (C).

To a solution of acetyl acetone (2.002 g, 20 mmol), 2-nitrophenylhydrazine (3.369 g, 22 mmol), in ethanol (60 ml) was added five drops of con. HCl and heated at 50 ^{o}C for 1 h. After confirming the formation of 3, 5-dimethyl-1-(2-nitrophenyl)-1H-pyrazole by TLC, ice cooled water is added in to the reaction mixture. The precipitate was filtered, washed with water and then hexane. The product will form as yellow precipitate, that precipitate has been filtered by normal filter paper. The product was recrystallized in ethanol. Brown solid, 95% (4.1265 g),

m.p 78 ^{o}C, IR (ν, cm^{-1}): 3444, 2923, 2104, 1612, 1527, 1359, 1118, 785. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, 1H, J = 8 Hz), 7.72 (t, 1H, J = 8 Hz), 7.59 (t, 1H, J = 8 Hz), 7.50 (d, 1H, J = 8 Hz), 6.03 (s, 1H), 2.25 (s, 3H), 2.19 (s, 3H). ^{13}CNMR (75 MHz, $CDCl_3$): δ 150.52, 146.43, 141.01, 133.23, 133.17, 129.54, 129.28, 125.12, 106.87, 13.50, 11.36. HRMS (ESI): m/z $[M + H]^+$ calcd for: $C_{11}H_{11}N_3O_2$ Calculated=217.2239, found= 217.2238.

2.2. Synthesis of 2-(3,5-dimethyl-1H-pyrazol-1-yl)aniline (D)

To a solution of 3, 5-dimethyl-1-(2-nitrophenyl)-1H-pyrazole (3.8 g, 17.49 mmol) in ethanol (50 ml) at 0 ^{o}C was added $SnCl_2$ (17.165 g, 76.07 mmol) portion wise over a period of 10 min. After complete addition of $SnCl_2$, the reaction mixture was slowly brought to room temperature and then refluxed for 4 h. After completion of the reaction, ice-cold water was added to the reaction mixture and neutralized with 20% NaOH. The compound was extracted with ethyl acetate, dried over anhydrous sodium sulphate concentrated under reduced pressure to get light brown powder. The product was pure enough and used as such in the next reaction without column chromatographic purification. Light brownish solid, 78%, (2.5548 g) m.p 79 ^{o}C, IR (ν, cm^{-1}): 3419, 2916, 1629, 1506, 1029, 746. ^{1}H NMR (400 MHz, $CDCl_3$):δ 8.41 (m, 4H, J = 4, 4 Hz), 7.25 (s, 1H), 5.42 (s, 2H), 3.54 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (75 MHz, CDCl3): δ 153.75, 148.64, 145.39, 134.13, 132.24, 129.94, 122.15, 121.26, 110.35, 18.42, 16.23. HRMS (ESI): m/z $[M + H]^+$ calcd for: $C_{11}H_{13}N_3$ Calculated=187.2410, found= 187.2411.

2.3. Synthesis of tridentate ligand [(E)-1-(((2-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)imino)methyl)naphthalen-2-ol]

A pressure tube was charged with 2-(3, 5-dimethyl-1H-pyrazol-1-yl) aniline (187.24 mg, 1 mmol), 2-hyroxy-1-naphthaldehyde (172.18 mg, 1 mmol), NH_4OAc (77. 08 mg, 1 mmol) and ethanol (3 ml) and was heated at 75 ^{o}C for 12 h. After confirming the formation of pyrazole derivative by TLC, ice cooled water was added in to the reaction mixture and was extracted with ethyl acetate, dried over anhydrous sodium sulphate concentrated under reduced pressure to get reddish brown semi solid as crude which was purified by column chromatography (silica gel) using pet.ether/ethyl acetate (80:20) to get pure compound. Reddish brown gummy compound, 94% (319 mg), m.p 72 ^{o}C, IR (ν, cm^{-1}): 3425, 2916, 1618, 1550, 1165, 746. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.55 (s, 1H), 9.15 (s, 1H), 8.02 (t, 1H, J = 8, 8 Hz), 7.81 (t, 1H, J = 12, 8 Hz), 7.73 (t, 1H, J = 8, 8 Hz), 7.57 (m, 3H, J = 8, 4 Hz), 7.42

(m, 2H, *J* = 8, 12 Hz), 7.19 (t, 1H, *J* = 8, 8 Hz) 7.07 (t, 1H, *J* = 12, 8 Hz), 2.32 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.40, 158.05, 143.33, 140.78, 136.30, 132.99, 132.51, 130.02, 129.20, 127.96, 127.32, 126.68, 123.56, 121.08, 120.43, 119.22, 117.63, 116.46, 109.20, 106.04, 13.57, 11.24. HRMS (ESI): m/z $[M + H]^+$ calcd for: $C_{22}H_{19}N_3O$ Calculated=341.4058, found= 341.4060.

2.4. Synthesis of catalyst F

In 50 ml round bottom flask $Cu(OAc)_2$ (074.42 mg, 0.3315 mmol) was suspended in 6 mL of deionized water and stirred for 4 h until a clear solution was obtained. To this solution (E)-1-(((2-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)imino)methyl)naphthalen-2-ol (230.44 mg, 0.675 mmol) in methanol (3 mL) was added drop wise and stirred for another 24 h. The reaction mixture was diluted with water, filtered, washed sequentially with water, methanol and *n*-hexane. Then dark greenish blue color crystal were formed and used for the reactions. The solid was crystallized in CH_2Cl_2 to get crystal whose structure was confirmed by single crystal XRD.

2.5. General experimental procedure for the preparation of triazole via azide alkyne coupling

To a solution of alkene (3 mmol) and azide (3 mmol) in 12 mL of a 1:1 water/*tert*-butanol mixture. Sodium ascorbate (0.3 mmol) was added, followed by copper ligand catalyst (0.03 mmol, 1 mol %). The reaction mixture was stirred vigorously at 80 ^{o}C for 5h. After the completion of the reaction as indicated by TLC, the reaction mixture was diluted with ethyl acetate and water and extracted three times with EtOAc. The combined organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to get the colorless solid which was further purified by column chromatography using silica gel and ethyl acetate: petroleum ether (1:9) as eluent gave the pure tri azole. The common triazole compounds were confirmed by comparing melting points and retention time in HPLC with authentic sample.

5-phenyl-1-tosyl-1H-1,2,3-triazole – Compound (3a)

White solid 90% yield. mp: 170 ^{o} C 1H NMR (400 MHz, CDCl3): δ = 2.36(s, 3H), 7.12 – 7.14 (m, 2H), 7.34 (s, 1H), 7.36-7.50 (m, J=7.0 HZ 4H), 7.86-7.88 (d, 2H) 8.35 (s,1H). 13C NMR (100 MHz, CDCl3): δ = 21.2, 125.9, 126.0, 127.6, 128.6, 129.4, 130.7, 138.3, 145.6, 146.0.

5-phenyl-1-(phenylsulfonyl)-1H-1,2,3-triazole – Compound (3b)

White solid 79% yield. mp: 138 ^{o}C 1H NMR (400 MHz, CDCl3): δ = 7.12 – 7.14 (m, 2H), 7.34 (s, 1H), 7.36-7.50 (m, J=7.0 HZ 4H), 7.86-7.88 (d, 2H) 8.35 (s,1H). 13C NMR (100 MHz, CDCl3): δ = 21.2, 125.9, 126.0, 127.6, 128.6, 129.4, 130.7, 138.3, 145.6, 146.0.

3-(Toluene-4-sulfonyl)-3H-[1,2,3]triazol-4-yl]-methanol Compound (3c)

Milk white solid 80% yield. 1H NMR (400 MHz, CDCl3): δ=2.44 (s, 3H), 3.86 (s, 2H) 4.81 (s, 1 H) 7.33 – 7.35 (t, 3 H), 7.93 – 7.96 (d, 1H). 13C NMR (100 MHz, CDCl3): δ = 22.1, 57.9, 126. 3, 128.7, 130, 130.1, 135.3, 138.3, 145.

5-phenyl-1-(p-tolyl)-1H-1,2,3-triazole – Compound (3d)

white solid (yield 85%). mp: 84^{o}C. 1H NMR (400 MHz, CDCl3): δ= 2.26(s, 3H), 7.25-7.47(m, 7H), 7.92(t, *J*=4.4 Hz, 2H), 7.96(s, 1H).13C NMR (100 MHz, CDCl3): δ= 17.8, 121.0, 125.7, 125.8, 126.7, 128.2, 128.8, 129.8, 130.3, 131.4, 133.6, 136.4, 147.5

1,5-diphenyl-1*H*-1,2,3-triazole – Compound (3e)

white solid (yield 98%). mp: 185-186^{o}C. 1H NMR (400 MHz, CDCl3): δ= 7.36(t, *J*=7.4 Hz, 1H) 7.43-7.48(m, 3H), 7.52-7.56(m, 2H), 7.80(t, *J*=4.6 Hz, 2H), 7.92(d, *J*=7.2 Hz, 2H), 7.92(d, *J*=7.2 Hz, 2H), 8.20(s, 1H), 13C NMR (100 MHz, DMSO): δ=119.5, 119.9, 125.3, 128.1, 128.6, 128.3, 129.8, 130.2, 136.6, 147.2.

1-(2-chlorophenyl)-4-phenyl-1*H*-1, 2, 3-triazole – Compound (3f)

brown solid (yield 98%). mp: 130 ^{0}C. 1H NMR (400 MHz, CDCl3): δ= 7.35(t, *J*=7.4 Hz, 1H), 7.42-7.46(m, 4H), 7.55-7.58(m, 1H), 7.62-7.65(m, 1H), 7.92(t, *J*=4.2 Hz, 2H), 8.19(s, 1H).13C NMR (100 MHz, CDCl3): δ= 121.5, 125.7, 127.6, 127.8, 128.2, 128.4, 128.8, 130.0, 130.6, 134.7, 147.4

2.6. General procedure for the Azide reduction

A 50ml round bottom flask was charged with Azide (3 mmol), sodium ascorbate (3.3mmol) and tBuOH : H_2O in 3:1 ratio (8mL) at room temperature. To this mixture copper catalyst (1mol%) was added. Then the reaction mixture was stirred vigorously for 6 hours at 80 ^{o}C. After the completion (monitored by TLC), the reaction mixtures were taken to separating funnel and the organic layer was extracted with EtOAc. Following evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on a silica gel column eluted with petroleum ether/EtOAc.

Benzenesulfonamide – Compound (4a)

Yield is 92%, m.p = 150 ^{0}C; IR (ν, cm^{-1}): 3340, 3240, 1550, 1440, 1330, 1150, 1090, 900; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.84 – 7.82 (m, 2H), 7.59 (m, 1H), 7.36 (m, 2H) ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 144.60, 132.27, 129.41, 126.04, 39.06

4-methylbenzenesulfonamide – Compound (4b)

Yield is 95%, m.p = 135 ^{0}C; IR (ν, cm^{-1}): 3390, 3310, 3250, 3110, 1555, 1460, 1320, 1155; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 12.47 – 12.40 (m, 1H), 12.09 (d, J = 7.8 Hz, 1H), 12.00 (s, 1H), 8.08 (s, 4H), 7.26 – 7.20 (m, 1H), 7.10 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 142.36, 141.83, 129.78, 126.09, 21.37

4-nitrobenzenesulfonamide – Compound (4c)

Yield is 95%, m.p = 179 ^{0}C; IR (ν, cm^{-1}): 3340, 3250, 1610, 1520, 1350, 1260, 850; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.21 (d, 2H, *J* = 8 Hz), 7.84 (d, 2H, *J* = 8 Hz), 7.05 (s, 2H);^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 154.53, 147.79, 127.39, 123.86

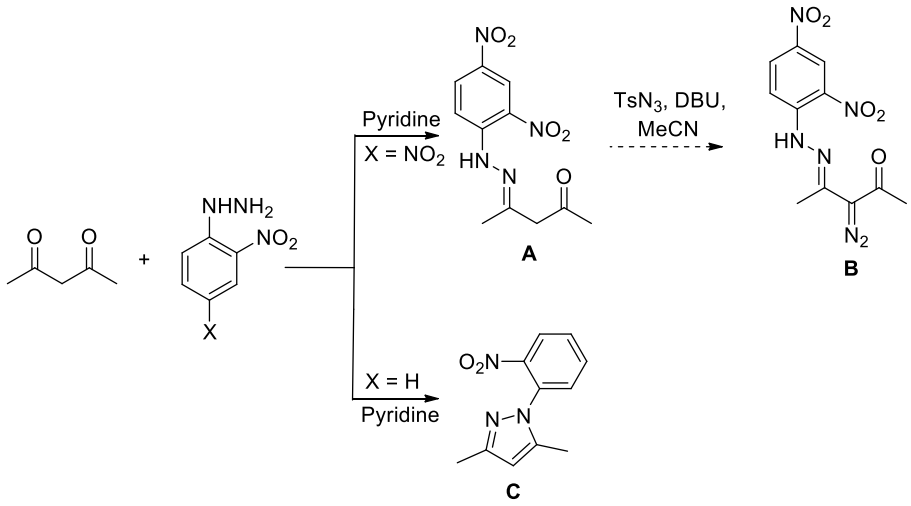
4-aminobenzenesulfonamide – Compound (4d)

Yield is 98%, m.p = 165.5 ^{0}C, IR (ν, cm^{-1}): 3450, 3360, 1352, 1172; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.46 (d, 2H, *J* = 8 Hz), 6.89 (s, 2H), 6.59 (d, 2H, *J* = 8 Hz), 5.8 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 152.38, 130.48, 127.9, 112.93

Benzyl amine – (Compound 4e) and **Aniline – (Compound 4f)** were confirmed by comparing with authentic sample

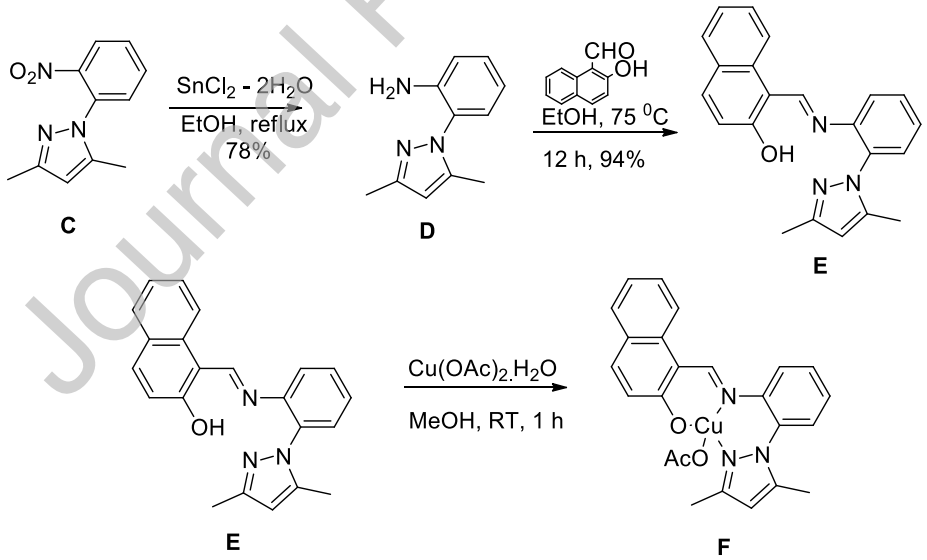
3. Results and discussion

In continuation of our research interest, [16] we attempted the synthesis of α-diazo hydrazones **B** by reacting nitro phenyl hydrazine and acetyl acetone followed by diazo transfer reaction. 2, 4-dinitrophenyl hydrazine reacted readily to give the corresponding hydrazone **A** in excellent yield while 2-nitrophenyl hydrazine gave pyrazole derivative **C** *via* Knorr pyrazole synthesis (**Scheme-1**). The difference in reactivity can be ascribed to the nucleophilicity of the nitrogen atoms in the two reactants. In 2, 4-dinitrophenyl hydrazine the two electron withdrawing NO_2 groups reduce the nucleophilicity of nitrogen *via* resonance. But, in the case of 2-nitrophenyl hydrazine the nitrogen is nucleophilic enough to undergo cyclization to give pyrazole in spite of presence of one NO_2.



Scheme 1

Even though we got disappointed with the unwanted product, we envisaged that the pyrazole deivative **C** with suitable substituent could serve as scaffold to obtain a novel class of atropisomerism based ligand in which the chiral axis passes through N-N bond. Accordingly, the nitro group in **C** was reduced with $SnCl_2$ in EtOH at reflux to get the corresponding amine in 78% yield. Treatment of amine with 2-hydroxy naphthaldehyde gave the tridentate ligand **E** in quantitative yields. [17]



Scheme 2: Synthesis of Tridentate ligand and catalyst

The tridentate ligand **E** was thoroughly characterized by the spectral data and single crystal X-ray technique. We were delighted to observe the pyrazole and phenyl rings to be in different planes and the angle of inclination of the two rings is more than 45°. This is highly

encouraging and by introducing more bulky substituent it would be possible to isolate atropisomers in pure form.

As the phenyl ring and pyrazole were in different planes, we assumed that the ligand might not act as tridentate ligand. To our surprise, reaction of the ligand with copper acetate resulted in the metal complexes which was readily crystallized in CH_2Cl_2. The single crystal X-ray diffraction shows that the complexes crystalizes with two molecule of CH_2Cl_2 and the ligand coordinate the metal through pyrazole N, imine nitrogen and phenoxide ion. The pyrazole and phenyl ring attain nearly planarity to coordinate to metal. The geometry of Cu^{2+} is not exactly tetrahedral or square planar

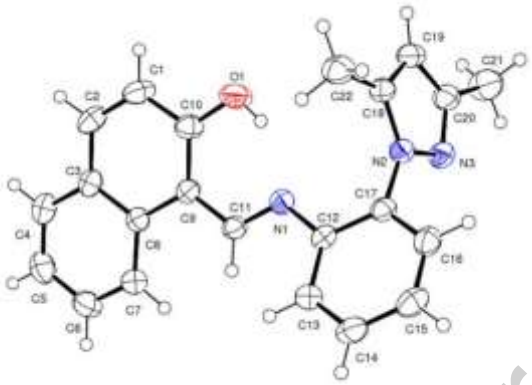


Fig.3: ORTEP diagram of the Tridentate ligand E

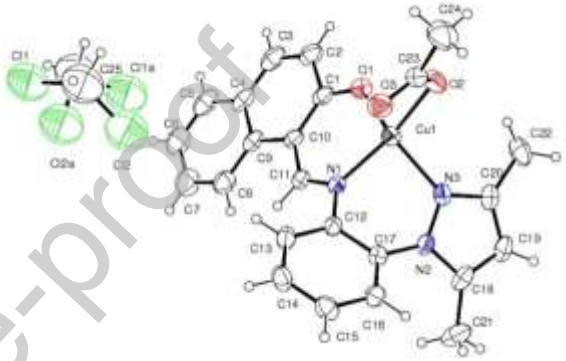


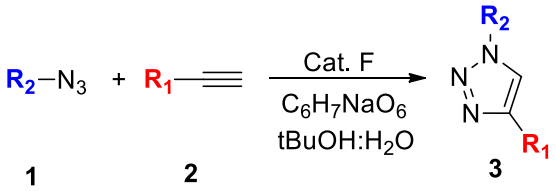
Fig.4: ORTEP diagram of the catalyst F

After successfully achieving the synthesis of new copper complex with tridentate ligand, we undertook the study of the application of the catalyst in organic tranformations. We have chosen the very well-known Cu(I) catalysed azide-alkyne cyclization to get triazole derivatives. Our attention was more on the [3+2] cycloaddition between alkyne and sulfonyl azide instead of aryl and alkyl azide since only a few reports are available on this cycloaddition.

Accordingly when toluene sulfonyl azide was treated with phenyl acetylene, sodium ascorbate in the presence of catalyst **F** (1 mol%) in solvent (t-BuOH:H_2O, 1:1), we obtained the corresponding triazoles in good yield. Surprisingly a small quantity of p-toluene sulfonamide was also obtained in the reaction. As expected benzyl azide and phenyl azide also gave the corresponding 1, 4-disubstituted triazoles derivative (**Table -1**). Even though Cu(II) is employed as the catalyst, Cu(I) is the reactive species in the reaction. Cu(II) is *in-*

situ reduced by sodium ascorbate to give Cu(I) species which promotes the azide alkyne coupling. [18]

Table 1 : Substrate Screening for Azide – Alkyne Cyclization [a]



Entry	Azide (R_2)	Alkyne (R^1)	Yield [b]
a	4-CH_3-$C_6H_4SO_2$-N_3	Ph-	90
b	$C_6H_5SO_2$-N_3	Ph-	79
c	4-CH_3-$C_6H_4SO_2$-N_3	-CH_2OH	80
d	4-CH_3-C_6H_4-N_3	Ph-	85
e	C_6H_5-N_3	Ph-	98
f	4-Cl-C_6H_4-N_3	Ph-	98

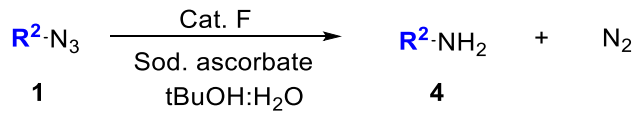
[a] Reaction condition: alkyne (3 mmol), azide (3 mmol), Sod.Ascorbate (0.3 mmol), cat. **F** (1 mol%), tBuOH : H_2O (1:1), 80 ^oC, 5 h. [b] Isolated yield by column chromatography

During the study of substrate scope, we also found the reaction to follow different pathway to give sulphonamide instead of azide – alkyne cycloaddition product. Azide reduction is the most widely used route to introduce amine functionality in the total synthesis [19]. Expecting our catalyst to serve as new protocol for azide reduction, we undertook the study of the catalyst to reduce azide to give the corresponding amide or amine. Accordingly, sulfonyl azide were heated at 80 ^oC with sodium ascorbate (1 equivalent) and the catalyst (1 mol%) in t-BuOH and H_2O as solvent. The corresponding sulphonamide were obtained in excellent yield with complete conversion (**Table- 2**). Since water is more acidic than tBuOH, we believe that the hydrogens for reduction are obtained from the water. Even though excellent yields were obtained for sulfonyl azide, this methodology furnished poor yields with aryl azide and alkyl azides (Entry e and f, Table 2).

In order to get insight into the mechanism, control experiments were carried out with p-toluene sulfonyl azide in the absence of catalyst and obtained the corresponding sulfonamide in considerably less yield (23%). Further, we also checked the possibility for

thermal decomposition under the reaction temperature, by heating the azide in the absence of catalyst and ascorbate. We found the compound to be stable under the reaction condition (solvent : tBuOH and H_2O, temperature: 80 ^oC) and no sulphonamide was observed. So we conclude that the formation of sulphonamide is not *via* the thermal decomposition of sulfonyl azide and there is role of catalyst in the reduction.

Table 2: Substrate Screening for Azide Reduction [a]



Entry	Azide (R_2)	Yield [b] (%)
a	$C_6H_5SO_2$-	95 (40)[c]
b	4-$CH_3C_6H_4SO_2$-	92 (23)[d]
c	4-$NO_2C_6H_4SO_2$-	95
d	4-NH_2 $C_6H_4SO_2$-	98
e	$C_6H_5CH_2$-	23
f	C_6H_5-	15

[a] Reaction condition: azide (3 mmol), Sod. Ascorbate (3.3 mmol), cat. F (1 mol%), tBuOH : H_2O (3:1, 6 mL : 2 mL), 80 ^oC, [b] Isolated yield by column chromatography, [c] Yield at 60 ^oC, [d] yield without catalyst

Based on the control experiments and experimental observations, we propose the following mechanism. Mechanistically, it is well proven that sodium ascorbate can reduce Cu(II) to Cu(I) by transferring one electron. We presume that Copper(I) gives one electron to the azide to furnish the intermediate **X** which can eliminate nitrogen *via* six member transition state to give the sulphonamide (**Fig.2**). Since we obtained poor yield of sulphonamide in the absence of copper catalyst, we believe that the transfer of electron from Cu(I) to azide is more facile than from sodium ascorbate to azide. Since the reduction of sulphonamide gave quantitative yield of the sulfonamide, we presume the sulfonyl group to facilitate the reduction *via* N_2 elimination.

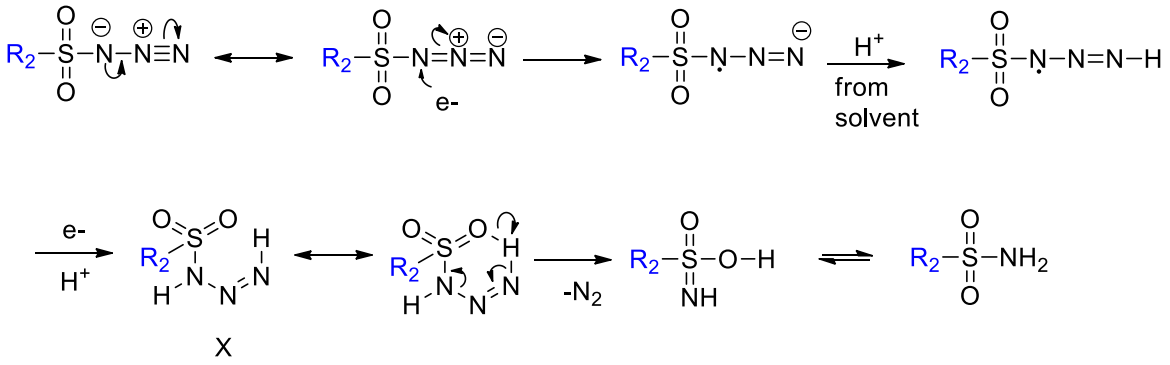


Fig.2: Plausible Mechanism

4. Conclusion

In conclusion, we have synthesized pyrazole based tridentate ligand and its copper(II) catalyst *via* a simple and efficient route. The ligand as well as the catalyst were well studied with spectroscopic techniques and single crystal XRD. We have also studied the efficiency of the catalyst for the azide-alkyne cycloaddition and azide reduction reactions. The ligand with suitable substituents will be separated into its enantiomers and the possibility to give chiral induction will be studied.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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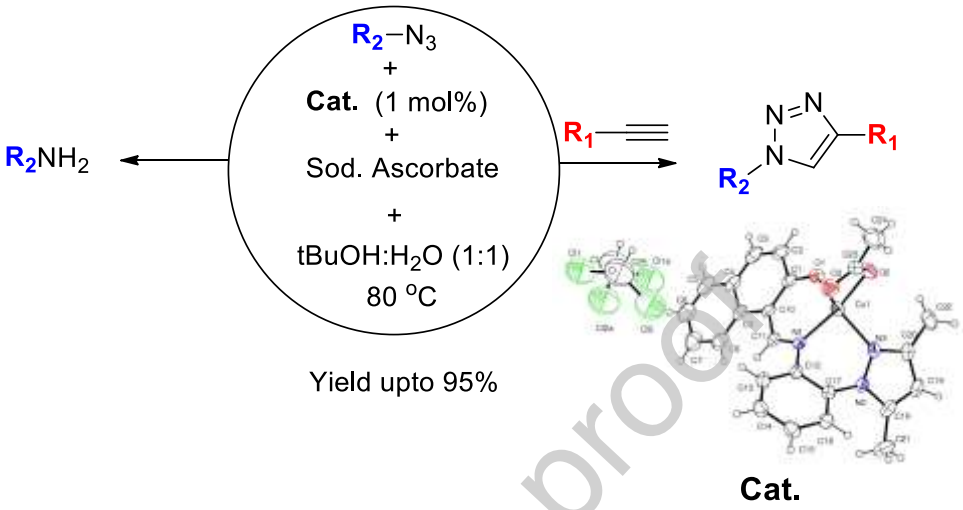
Graphical Abstract



Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.