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Cu(II)@Luviset clear as recyclable catalyst for the formation of C-C bond in homo-coupling of terminal alkynes

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Commercial copolymer Luviset clear (**L1**), an environment-benign and efficient ligand, was used to facilitate the catalytic performance of $Cu(NO_3)_2$ for homo-coupling of terminal alkynes. A series of substituted aromatic and aliphatic terminal alkynes were investigated. It was found that $Cu(NO_3)_2$@**L1** can catalyze the C-C coupling reactions without any other base, and the corresponding diynes are generated in good to excellent yield. X-ray photoelectron spectroscopy was used to study the reaction mechanism, and the results evidence a Cu(II)/Cu(I) catalytic system. Additionally, the catalyst can be easily separated and reused without showing significant loss of catalytic activity.

Introduction

Recently, polymer-bound metal catalysts have attracted much attention for environment-benign synthesis.[1] With the immobilization of transition metals on polymers, there are advantages in terms of eco-friendliness, air and moisture resistance, as well as catalyst stability. As quantified by theoretical calculations, the use of polymer as ligand is suitable for a variety of metals.[2] It is envisaged that the polymer-bound metal catalysts can be easily recovered and recycled.[3] For example, Han's group reported a soluble polymer-bound ligand-accelerated catalytic system for asymmetric dihydroxylation,[4] and Bergbreiter et al. prepared an effective soluble polymer-bound Pd(II) catalyst for Heck reactions.[5] Nevertheless, most of the reported works have shortcomings such as high metal cost, complicated reaction steps, and rigorous demand of operational skills.[6]

Copper (Cu), a typical representative of transition metals, is well accepted as one of the most prominent, important, and promising catalysts for its versatility, low toxicity, and low cost.[7,8] Cu-based materials are widely used as catalysts for synthesis of natural products,[9] agrochemicals,[10] medicine molecules,[11,12] and organic functional materials.[13] In particular, the formation of C-C bonds catalyzed by Cu-based catalysts is of great interest in organic synthesis.[14-17] One example is the use of Cu(I) for the oxidative coupling of two phenylacetylene molecules to yield 1,3-diynes,[18]

which are building blocks of natural products,[19,20] pharmaceuticals[21,22] (e.g. anti-HIV[23] and antitumor[24]), polymers,[25,26] and organic/inorganic composites.[27,28]

Numerous efforts have been devoted to the development of methods that are facile, efficient, and eco-friendly for preparation of conjugated diynes.[29-37] The process is usually performed either at high temperature without any ligand[32] or under mild reaction conditions with the assistance of ligands.[38] Investigations were performed on the selection of ligands, solvents, oxidants, and Cu catalysts (e.g., $CuBr_2$/enaminone/pyrrolidine,[30] $CuCl_2$/TMEDA,[33] CuI/$[DMIM]Me_2PO_4$/$NH_3 \cdot H_2O$,[34] $Cu(OH)x$/OMS-2,[35] $CuCl$,[36] and $CuCl_2$/KF–Al_2O_3/ball mill system[37]).

As far as we know, there is no report on the use of polymer as a metal ligand for the homo-coupling of terminal alkynes. Herein, we describe a highly efficient protocol for the synthesis of conjugated 1,3-diynes catalyzed by $Cu(NO_3)_2$ in the presence of a water-soluble and nonionic co-polymer of N-vinylpyrrolidone, methacrylamide and N-vinyl imidazole (i.e. Luviset Clear (**L1**); its molecular formula is displayed in Figure 1). The as-developed catalyst system denoted hereinafter as $Cu(NO_3)_2$@**L1** facilitates homo-coupling of terminal alkynes under mild conditions without using any other base.
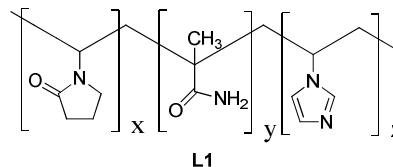
Fig. 1 The molecular formula of **L1**.

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Experimental

Materials

The solvents and chemicals were of analytical grade and used without further purification. Phenylacetylene (98 wt.%), $Cu(NO_3)_2$, Luviset clear (19 wt.%) were purchased from Shanghai Aladdin Chemical Reagent Company (Shanghai, China). Ethanol, toluene, acetone, acetonitrile, dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) and other chemicals were from Energy Chemical Reagent Company (Shanghai, China) .

Homo-coupling of terminal alkynes

The reactions were conducted as follows: A mixture of terminal alkyne (1 mmol), $Cu(NO_3)_2$ (4 mol %, 7.5 mg), **L1** (128 mg), and DMSO (2 mL) were put into a sealed Schlenk tube (10 mL) and stirred at 100 °C for a desired period of time. The reaction was monitored by thin layer chromatography (TLC). Afterwards, the reaction mixture was cooled to room temperature. The catalyst was recovered by filtration, and washed thoroughly with ethyl acetate. The combined organic layer was dried by anhydrous sodium sulfate, and the crude product was purified by column chromatography.

Characterization

The as-prepared organic compounds were characterized by ^1H NMR and ^{13}C NMR spectra. ^1H NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ [using $(CH_3)_4Si$ (for ^1H, δ = 0.00) as internal standard]. ^{13}C NMR spectra were performed on a Bruker Avance 400 spectrometer in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, δ = 77.00) as internal standard]. The relevant physical properties, ^1H NMR and ^{13}C NMR spectra and mass analysis data (obtained over USA Thermo Finnigan Corporation, MAT 95 XP) of the products are provided in Electronic Supporting Information (ESI). The valence of Cu during the reaction was examined by X-ray photoelectron spectroscopy (XPS, thermofisher-ESCALab 250, Al Kα (1486.6 eV)).

Results and discussion

For initial optimization of the reaction conditions, phenylacetylene was chosen as a model substrate as depicted in Table 1. The reactions were carried out at 100 °C for 4 h in different solvents, using $Cu(NO_3)_2$ (4 mol %, 7.5 mg) as catalyst and **L1** (128 mg) as ligand. It is observed that among the solvents, DMSO (Table 1, entry 1) shows the highest product yield (Table 1, entries 2-9).

It is found that the product conversion is sensitive to temperature change (Table 1, entries 10-13). There is significant decrease of product yield when the reaction temperature is lowered to 25 °C (Table 1, entry 10). The result is expected because it is well known that reaction temperature plays a significant role in chemical reactions.[39] As for the effect of reaction time, there is a gradual increase of product yield with time (Table 1, entries 14-18).

Table 2 depicts the effects of the change in $Cu(NO_3)_2$/**L1** mass ratio on the reaction. When the reaction is conducted without **L1**, the product yield is only 37% (Table 2, entry 2), reflecting the undelaying role of L1. From the results of $Cu(NO_3)_2$/**L1** variation (Table 2, entries 1, 3-5), the optimal $Cu(NO_3)_2$/**L1** mass ratio is 1:2 (Table 2, entry 1). Then, we sought to identify some other ligands that could promote the homo-coupling of terminal alkyne. As

depicted in Table 3, a number of ligands are screened (entries 2-5), ligands **L2-L5** provid higher yield of the desired product under the same conditions as **L1**. Nevertheless, it is found that the use of **L1** results in the most effective improvement for homo-coupling of the terminal alykne.
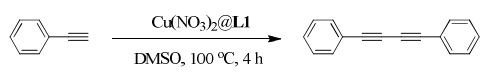
Next, we tested the influence of different copper salts as the catalyst on the yields. In accordance with expectation, no reaction is occurred without a copper salt under the identical conditions. (Table 2, entry 1). Form the results, we can easily find that the anion part has a significant impact on the catalytic activity, and $Cu(NO_3)_2$ shows better catalytic activity than other Cu-catalysts (Table 2, entries 2-10).

According to the data acquired so far, the optimized reaction conditions are determined as: a mixture of terminal alkyne (1 mmol), $Cu(NO_3)_2$ (4 mol %, 7.5 mg), **L1** (128 mg), and DMSO (2 mL) were stirred for a designated time at 100 °C with air atmosphere in a sealed Schlenk tube (10 mL) .

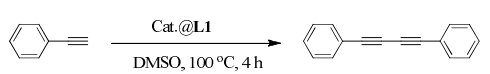**Table 1** Optimization of conditions for homo-coupling of terminal alkynes[a]

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	**DMSO**	**100**	**4**	**97**
2	Toluene	100	4	31
3	DMF	100	4	87
4	Acetone	100	4	23
5	THF	100	4	39
6	CH_3CN	100	4	78
7	1,4-Dioxane	100	4	48
8	H_2O	100	4	62
9	Ethanol	100	4	66
10	DMSO	25	4	trace
11	DMSO	40	4	27
12	DMSO	60	4	53
13	DMSO	80	4	86
14	DMSO	100	0.5	trace
15	DMSO	100	1	34
16	DMSO	100	2	46
17	DMSO	100	3	73
18	DMSO	100	5	97

[a] Reaction conditions: phenylacetylene (1 mmol), catalyst ($Cu(NO_3)_2$ (4 mol %, 7.5 mg), and **L1** (128 mg). [b] Isolated yield.

Table 2 Effect of the change in Cu(NO$_3$)$_2$/L1 mass ratio[a]

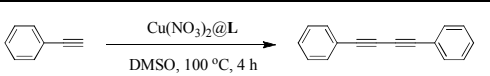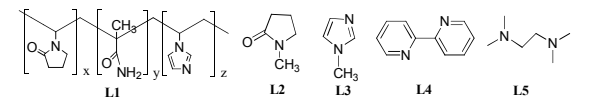| Entry	Cu(NO$_3$)$_2$	L	Mass ratios	Yield (%)[b]
1	7.5 mg	128 mg	1:2	97
2	7.5 mg	---	1:0	37
3	7.5 mg	32 mg	2:1	51
4	7.5 mg	64 mg	1:1	76
5	7.5 mg	192 mg	1:3	81

[a] Reaction conditions: phenylacetylene (1 mmol), catalyst (Cu(NO$_3$)$_2$ and **L1**), DMSO (2 mL), 100 °C, 4 h. [b] Isolated yield.
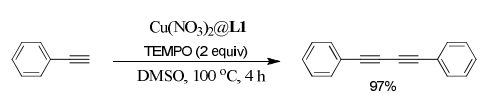
Table 2 Effects of various copper salts [a]

Entry	Catalyst	Yield (%)[b]
1	None	o
2	**Cu(NO$_3$)$_2$**	**97**
3	CuCl$_2$	73
4	CuBr$_2$	72
5	Cu(acac)$_2$	52
6	CuSO$_4$	82
7	Cu(OAc)$_2$	70
8	CuI	77
9	CuBr	86
10	CuCl	91

[a] Reaction conditions: phenylacetylene (1 mmol), catalyst(4 mol %) and **L1**, DMSO (2 mL), 100 °C, 4 h. [b] Isolated yield.

Table 3 Effects of different Ligands[a]

Entry	Ligand	Mass	Mass ratios	Yield(%)[b]
1	**L1**	**128 mg**	**1:2**	**97**
2	L2	7.9 mg	1:2	88
3	L3	6.6 mg	1:2	78
4	L4	12.5 mg	1:2	64
5	L5	9.3 mg	1:2	81

[a] Reaction conditions: phenylacetylene (1 mmol), catalyst (Cu(NO$_3$)$_2$ and L), DMSO (2 mL), 100 °C, 4 h. [b] Isolated yield.

Table 4 Homo-coupling of terminal alkynes catalyzed by Cu(NO$_3$)$_2$@L[a]

Entry	Alkyne	Products		Time (h)	Yeild (%)[a]
1			2a	4	97
2			2b	4	95
3			2c	4	91
4			2d	4	89
5			2e	4	89
6			2f	4	92
7			2g	4	90
8			2h	4	91
9			2i	4	85
10			2j	4	83
11			2k	12	74
12			2l	4	73
13			2m	4	70

[a] Reaction conditions: phenylacetylene (1 mmol), catalyst (Cu(NO$_3$)$_2$ and **L1**), DMSO (2 mL), 100 °C, 4 h. [b] Isolated yield.

Under the optimized conditions, a large number of terminal alkynes were tested for the production of the corresponding diynes (Table 4). The results reveal that the Cu(NO$_3$)$_2$**@L1** system can be applied to reactants with different functional groups, and the product yield is highly dependent on the nature of substituted groups.[40]

We investigated the general applicability of the system to aromatic acetylenes decorated with a variety of electron-donating and electron-withdrawing groups. It is noted that the system facilitates the homo-coupling of aromatic acetylenes with electron–donating groups such as -CH$_3$, -NH$_2$ and -OCH$_3$, leading to satisfactory yields (89-95%) within 4 h (Table 4, entries 2–8). Whereas electron–withdrawing substituents (–F and –CF$_3$) induce slightly lower reactivity (Table 4, entries 9 and 10), owing to the effect of nucleophilicity.[41]

It is observed that *para*–methylphenyl acetylene gives the highest product yield, followed by *meta*–methylphenyl acetylene and *ortho*–methylphenyl acetylene (Table 4, entries 2–4), plausibly a result of difference in steric hindrance.[42] Specifically, the reactivity of mono–substituted aryl alkynes follows the sequence: *para* >

meta > o*rtho*.[43,44]

Encouraged by the efficiency of the reaction protocol, we examined the homo-coupling of aliphatic terminal alkynes, displaying lower reaction activity and reaction rates (Table 4, entry 11), presumably due to the weaker acidity of aliphatic terminal alkynes in comparison with those of aromatic counterparts.[20] As for the heteroatom alkynes (Table 4), the product yields are between 73% and 70% due to the partial carbonization of substrates (Table 4, entries 12–13).[45]

We determined the reusability of the catalyst that can be conveniently recovered by filtration. After thorough washing with ethyl acetate, the recovered catalyst was dried in an oven at 60 °C, and reused for the next cycle. The results demonstrate that the catalyst can be reused for at least 5 times without showing significant loss of the catalytic activity (Figure 2). The results indicate the supreme stability of the Cu(NO$_3$)$_2$@**L1** catalyst.
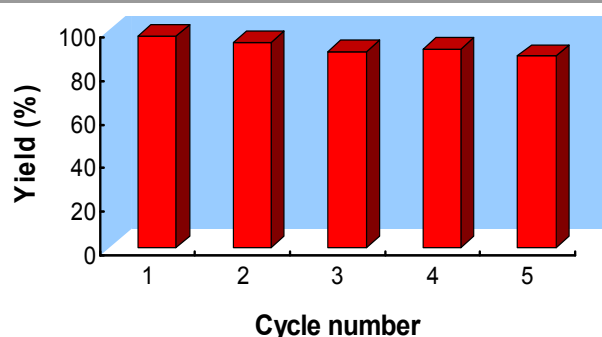

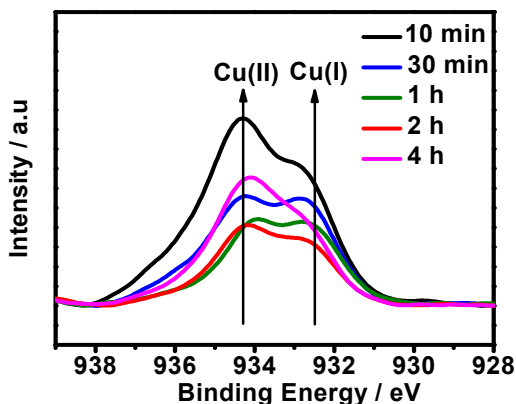**Fig. 2** Recyclability test of the catalytic system.

Fig. 3 Cu 2p XPS spectra of the polymer-Cu species after different periods of reaction time.

To probe the reaction mechanism, we monitored the oxidation states of Cu by XPS. As shown in Figure 3, there are two peaks located at 932.5 and 934.3 eV assigned to Cu(I) and Cu(II),[51-53] respectively. By prolonging the reaction time, there is an increase and then gradual decline of Cu(I)/Cu(II) peak intensity ratio. The
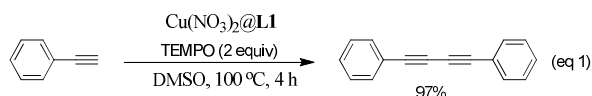
result demonstrates that the Cu element undergoes a cyclic process: first the formation and then the consumption of Cu(I) species during the homo-coupling reaction of terminal alkyne.

We also introduced the radical inhibitor 2,2,6,6-tetramethyl-piperidyl-1-oxyl (TEMPO) to the reaction media with the product yield of 97% (Eq. 1). It means that the homo-coupling of terminal alkynes as catalyzed by Cu(NO$_3$)$_2$@L1 does not follow the acetylenic radical mechanism but rather an electron transfer process.[46] Based on the mechanistic pathway reported in the literature,[47,48] a possible mechanism is described in Scheme 1. At the initial stage, the triple bond is activated by Cu(II) and alkynylcuprate is formed which readily reacts with the terminal triple bond to produce dimeric copper acetylide as a pivotal intermediate,[49] along with the formation of coupling products and Cu(I) species through a reductive elimination step.[50] The regeneration of Cu(II) is fulfilled by the oxidation of Cu(I) species with oxygen in air.[48,51]
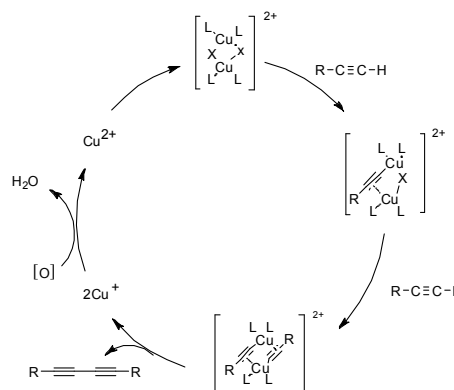
Scheme 1. Possible catalytic mechanism of the homo-coupling rreaction.

Conclusions

Cu(NO$_3$)$_2$@**L1** was developed as a simple, low-cost, and efficient catalyst for the homo-coupling of terminal alkynes. The corresponding conjugated 1,3-diynes were synthesized with satisfactory yield without the need of a base or oxidant. A reaction mechanism based on the Cu(II)/Cu(I)) cyclic route was discussed and evidenced by XPS results. The facile, effective, and inexpensive Cu(NO$_3$)$_2$@**L1** catalyst has high potential for industrial applications.

Acknowledgements

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