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Experimental Evidence for the Involvement of Dinuclear Alkynylcopper(I) Complexes in Alkyne–Azide Chemistry

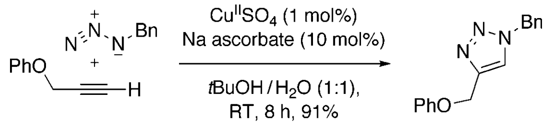
Benjamin R. Buckley, Sandra E. Dann, and Harry Heaney*[a]

Abstract: Dinuclear alkynylcopper(I) ladderane complexes are prepared by a robust and simple protocol involving the reduction of $Cu_2(OH)_3OAc$ or $Cu(OAc)_2$ by easily oxidised alcohols in the presence of terminal alkynes; they function as efficient catalysts in copper-catalysed alkyne–azide cycloaddition reactions as predicted by the Ahlquist–Fokin calculations. The same copper(I) catalysts are formed during reactions by using the Sharpless–Fokin protocol. The experimental results also provide evidence that sodium ascorbate functions as a base to deprotonate terminal alkynes and additionally give a convincing alternative explanation for the fact that the Cu^I-catalysed reactions of certain 1,3-diazides with phenylacetylene give bis(triazoles) as the major products. The same dinuclear alkynylcopper(I) complexes also function as catalysts in cycloaddition reactions of azides with 1-iodoalkynes.

Keywords: alkynes · azides · catalysis · click chemistry · copper

Introduction

The rapid development of the use of organocopper reagents in organic synthesis over the past fifty years has been comprehensively documented in a number of reviews.[1] In particular, 1,3-dipolar cycloaddition reactions, pioneered by Huisgen,[2] have re-emerged recently as a major area of research as a result of the search for atom efficiency,[3] especially the so-called click reactions that involve terminal alkynes and high energy organic azides that were found by Sharpless and Fokin[4a] and Meldal[4b] and their co-workers to be accelerated by the use of copper(I) catalysts. The majority of the examples of copper-catalysed alkyne–azide cycloaddition (CuAAC) reactions reported have involved the reduction of copper(II) to copper(I), for example, by using sodium ascorbate as shown in Scheme 1.[4a] Thermal 1,3-dipolar cycloaddition reactions normally give 1:1 mixtures of regioisomers, whereas the copper-catalysed reactions are highly regioselective and give 1,4-disubstituted triazoles.



Scheme 1. The CuAAC reaction.

Additional reactions have also been reported that involve the direct introduction of copper(I) salts,[5] the oxidation of metallic copper to copper(I),[6] or the use of Cu^0/Cu^{II} as a method of generating copper(I).[7] These reactions continue to find wide use in organic synthesis, biology and materials science,[8] and the reviews on the subject indicate that the copper(I) oxidation state is required.[9] However, although there is an explicit statement that copper(II) salts do not catalyse the reactions,[4b] there are a limited number of reports of the direct use of copper(II) salts.[10] A careful kinetic investigation of the copper(I)-catalysed reaction of phenylacetylene and benzyl azide[11] revealed a second-order dependence on copper that required a modification of an earlier mechanism.[12] More recent calculations, based on the requirement of two copper atoms in the transition-state complex, gave a significantly reduced value for the activation energy for the reaction of methyl azide and propyne coordinated to two copper(I) atoms, each of which had identical spectator ligands.[13] We noted that hydrogen peroxide was used to quench the aliquots taken to obtain the kinetic data;[11] these measurements exclude the possibility that copper(II) can catalyse CuAAC reactions and encouraged us to

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[a] Dr. B. R. Buckley, Dr. S. E. Dann, Prof. Dr. H. Heaney
Department of Chemistry
Loughborough University
Loughborough, Leicestershire
LE11 3TU (UK)
Fax: (+44) 1509-223925
E-mail: h.heaney@lboro.ac.uk

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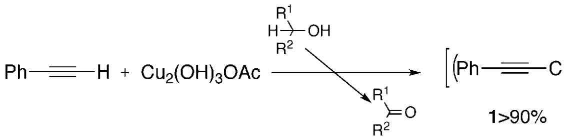
investigate the use of copper(II) hydroxyacetate as a precatalyst in microwave-assisted CuAAC reactions carried out at high temperatures in acetonitrile. That investigation revealed the involvement of polymeric alkynylcopper(I) ladderane complexes.[14] As part of our ongoing interest in copper(I)-catalysed reactions, we were interested to obtain experimental evidence to support the calculated involvement of dinuclear copper(I) complexes in CuAAC reactions carried out using the mild ambient temperature, *tert*-butanol/water reaction conditions.[4a] It is informative to note that the Meldal method uses Hünig's base and sodium hydroxide, whereas the Sharpless–Fokin CuAAC protocol uses a large excess of sodium ascorbate: we reasoned that the comment made by Knöpfel and Carreira,[15] that ascorbate may have an important role in addition to that involved in reducing Cu^{II}, is justified. We now report results relating to both of the above issues. We were also intrigued by the impressive recent discovery of copper(I)-catalysed reactions of organic azides with 1-iodoalkynes that result in the formation 1,4-disubstituted-5-iodotriazoles,[16] and report additional data on the use of alkynylcopper(I) ladderane complexes as catalysts in reactions of organic azides with 1-iodoalkynes.

Results and Discussion

In connection with CuAAC reactions carried out under mild reaction conditions and predicted by Ahlquist and Fokin to involve an intermediate with two Cu^{I} atoms,[13] we noted that a number of yellow or orange organocopper(I) species are known and have short Cu^{I}–Cu^{I} distances; some are stabilised by ligands.[17] Polymeric alkynylcopper(I) complexes have been known for many years,[18] and were originally prepared by the interaction of copper(I) iodide with alkali metal derivatives of terminal alkynes.[19] Although a number of other methods have been used to prepare alkynylcopper(I) derivatives, the majority involve reactions of copper(I) salts with terminal alkynes or derivatives.[20] We have prepared alkynylcopper(I) derivatives as co-products in Glaser reactions of terminal alkynes by using copper(II) hydroxyacetate in acetonitrile.[14] The detailed structure of the yellow phenylethynylcopper(I) $[\{PhCCCu\}_2]_n$ (**1**), determined by using X-ray powder diffraction (XRD), was reported recently by Che and co-workers[21] and is shown to have a ladderane structure in which the phenylethynyl residues are linked to two copper(I) atoms that are separated by distances of between 2.49 and 2.83 Å, ideally positioned to take part in click CuAAC reactions.

The use of easily oxidised alcohols as reducing agents in the presence of metal salts has been known for many years. For example, isopropanol is used together with aluminium isopropoxide in the Meerwein–Pondorf–Verley reduction of ketones,[22] and more recently in the reduction of a phenanthroline–copper(II) complex to the related copper(I) complex.[23] Less well known is the reduction of aromatic nitrocompounds by ethanol in the presence of iron/iron(II) chloride.[24] We found that a suspension of copper(II) hydroxyacetate, characterised by XRD,[26] with phenylacetylene in ethanol gave a yellow insoluble product after several days at 32 °C. Comparison of the XRD pattern (see the Supporting Information) of the yellow insoluble product with the expected XRD pattern calculated from the crystal structure reported by Che and co-workers,[21] confirmed the structure as ladderane polymer **1**, formed in 92 % yield. We also found that compound **1** was formed in a quantitative yield in methanol at around 32 °C after 2 d or after 14 h in isopropanol at 80 °C. The filtrate in the latter reaction was shown by gas chromatography to contain acetone. Not surprisingly, a sealed suspension of copper(II) hydroxyacetate and phenylacetylene in $tBuOH/H_2O$ in the absence of air and at ambient temperature is essentially unchanged after one year. However, a suspension of copper(II) hydroxyacetate in *t*BuOH at 32 °C was partially converted, after 120 d, into ladderane polymer **1** in the presence of phenylacetylene; 1,4-diphenylbuta-1,3-diyne was isolated from that reaction in 50 % yield. The methods that involve the use of alcohols as reductants are general and we were able to prepare yellow copper(I) derivatives from a range of terminal alkynes (Scheme 2), as shown in the Supporting Information.

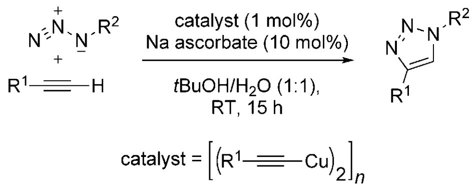


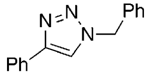
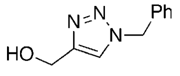
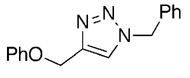
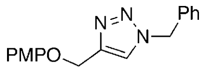
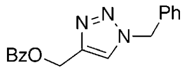
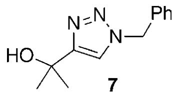
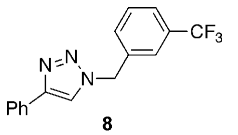
Scheme 2. Formation of Cu^{I} ladder polymers.

The amounts of Glaser products formed in the reactions are low if reactions are carried out in closed vessels in the absence of air. The production of an unidentified copper(I) catalyst from a copper(II) salt in easily oxidised alcohols was also reported recently.[26] A qualitative indication of the rates of reduction of copper(II) hydroxyacetate in alcohols is given by the fact that the reactions are fastest in methanol and slowest in isopropanol. The copper(I) derivative from 3-hydroxy-3-methylbut-1-yne was not formed by using copper(II) hydroxy acetate in methanol: a red precipitate, which was not investigated, was formed, presumably because the alkyne, a protected form of ethyne, was deprotected by hydroxyl ions. However, 3-hydroxy-3-methylbut-1-ynylcopper(I) must have been formed in the reaction shown below (compound **7** in Table 1, entry 11). Alkynylcopper(I) derivatives, for example, compound **1** can be prepared from copper(II) acetate in methanol, in reactions that proceed more slowly than the reactions that use copper(II) hydroxyacetate. We assume that the acetic acid produced in reactions that use copper(II) acetate retards the reduction process. Compound **1** was not formed when a mixture of copper(II) sulfate pentahydrate and phenylacetylene was allowed to stand in methanol at ambient temperature over a period of 30 d.

Phenylethynylcopper(I) is a stable material and forcing reaction conditions are required in Stevens–Castro reac-

Table 1. CuAAC reactions with dinuclear copper(I) ladderane complexes.[a]

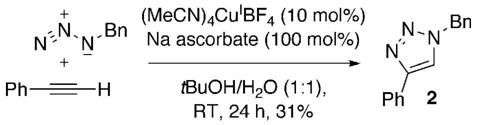


Entry	Product	Yield[b] [%]
1	 **2**	79
2		76[c]
3	 **3**	77
4	 **4**	78
5		81[c]
6		75[d]
7		70[e]
8	 **5**	91
9		98[d]
10	 **6**	89
11	 **7**	86[e]
12	 **8**	78

[a] General conditions: see table scheme. [b] Isolated yield. [c] Conditions: copper(II) sulfate (1 mol%), sodium ascorbate (10 mol%), *tert*-butanol/water (1:1), RT, 15 h. [d] Reaction carried out in the absence of sodium ascorbate. [e] Crossover experiment with 3-(4-methoxyphenoxy)-prop-1-ynylcopper(I) (**10**; 1 mol%) as the catalyst.

tions; for example, 2-phenylindole was obtained in 89% yield when 2-iodoaniline and phenylethynylcopper(I) were heated together in dimethylformamide at 175 °C.[27] We also found phenylethynylcopper(I) to be very stable and 1,4-diphenylbuta-1,3-diyne was formed in 62% yield only when we heated a suspension in dimethylformamide at reflux for 24 h. A yellow material, which was assumed to be a Cu^I π-complex of 1,4-diphenylbuta-1,3-diyne, was reported to give 1,4-diphenylbuta-1,3-diyne after being heated under reflux in dimethylformamide;[28] it is likely that that material was also phenylethynylcopper(I).

In connection with the use of sodium ascorbate, we noted that tetrakis(acetonitrile)copper(I) (10 mol%) in toluene does not function as a catalyst in CuAAC reactions.[29] Acetonitrile is known to be a strong ligand for copper(I),[30] and we anticipated that acetonitrile might, as a result, also act as a competing ligand in the CuAAC process. We also reasoned that an added base would be required. A reaction of phenylacetylene with $[Cu^I(MeCN)_4]$ (5 mol%) in the presence of sodium ascorbate gave a small amount of a yellow precipitate. When we used $[Cu^I(MeCN)_4]$ as the source of copper(I) in a reaction of phenylacetylene and benzyl azide in *t*BuOH/H_2O, together with an excess of sodium ascorbate, we obtained the CuAAC product (**2**), but in only 31% yield after 24 h. We presume that the low yield shown in Scheme 3 resulted from the strong ligation of acetonitrile to copper(I) and that only a very low concentration of **1** was formed. Importantly, the result shown in Scheme 3 established that sodium ascorbate initiates the formation of an alkyne–copper(I) ladderane complex by facilitating the deprotonation of the required amount of alkyne. In connection with this, it is interesting to note that CuAAC reactions can be carried out by using tetrakis(acetonitrile)copper(I) in the presence of a series of triazolylmethylamine derivatives; we conclude that the amine acts as a base to deprotonate the required amount of alkyne.[31]



Scheme 3. CuAAC reaction with $Cu^I(MeCN)_4$ as the source of Cu^I.

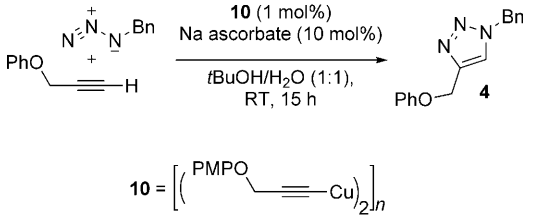
We have prepared **1** by using the Owsley–Stevens protocol,[20d] and by reducing copper(II) sulfate in *t*BuOH/H_2O with sodium ascorbate in the presence of phenylacetylene. A reaction of PhCCH with Cu_2O in MeCN to which we added five drops of aqueous NH_3 also gave a quantitative yield of **1**. The materials prepared by each of these methods have been used successfully as catalysts in the CuAAC reactions reported below.

We next carried out a series of reactions at ambient temperature in which we stirred a suspension of a catalytic quantity of an alkynylcopper(I) derivative, the appropriate alkyne and benzyl azide (BnN_3) in *t*BuOH/H_2O (1:1) to which we added an excess of sodium ascorbate. We were pleased to obtain the anticipated CuAAC derivatives (**2**–**8**) in excellent yields after about 15 h, as shown in Table 1.

We also carried out reactions of phenylpropargyl ether and phenylacetylene, each with BnN_3, under the conditions used in the original report by Sharpless, Fokin and co-workers (Table 1, entries 2 and 5).[4a] We noted that a transient yellow colour persisted for about 30 s when using 1 mol% of copper(II) sulfate, which was soon obscured by a white suspension. When we carried out reactions with larger amounts of copper(II) sulfate, the reaction mixtures remained lemon yellow at the end of the reaction times and the yields of **2** were, within experimental error, constant. In the latter reactions, we were able to isolate alkynylcopper(I) ladderane complexes. The yield of the CuAAC products in our hands were comparable to those obtained by using either 3-phenoxyprop-1-ynylcopper(I) (**9**) or **1** as the catalyst.

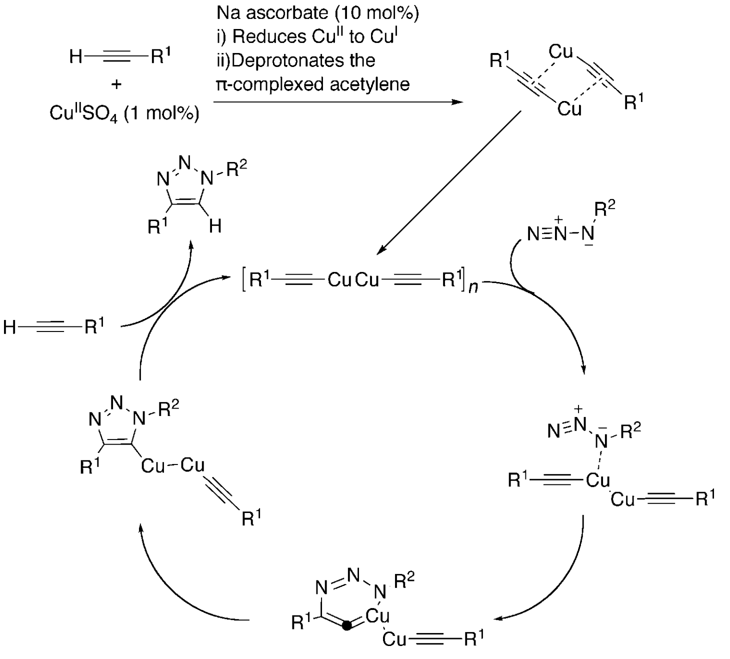
When we carried out a reaction of 4-methoxyphenylpropargyl ether with BnN_3 in the presence of 3-(4-methoxyphenoxy)prop-1-ynylcopper(I) (**10**) without adding sodium ascorbate, we obtained the anticipated triazole in an excellent yield. This reaction shows that once the dinuclear ladderane complex is formed, external deprotonation of the alkyne is no longer required for the catalytic cycle, as confirmed by our earlier deuteriation experiment.[14]

Crossover experiments in which an alkyne, such as phenylpropargyl ether, and benzyl azide were used together with 1 mol% of a catalyst (e.g., **10**) established that the alkyne is incorporated into the catalyst to produce the isolated product (Scheme 4). The contaminant derived from the initial ladder catalyst (triazole **5**) would be produced in no more than 1% yield (see the Supporting Information).

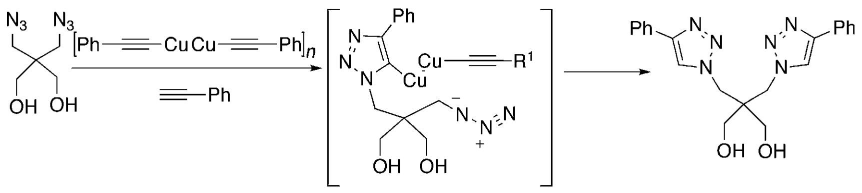


Scheme 4. Crossover experiment.

Our experimental results establish that isolable dinuclear copper(I) ladderane complexes act as efficient catalysts under the mild reaction conditions originally formulated by Sharpless, Fokin and co-workers,[4a] and that they fulfil the experimentally determined[11] and calculated[13] requirements for a dinuclear copper(I) complex. We propose a minor change to the previously published mechanism of CuAAC reactions that requires sodium ascorbate to deprotonate an initial copper(I) π-complexed alkyne that then collapses to the true catalyst depicted in Scheme 5.



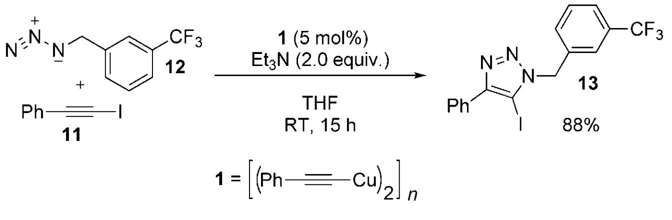
Scheme 5. Mechanism of the CuAAC reaction with dinuclear Cu^{I} ladderane complexes.



Scheme 6. Cu^{I}-catalysed reaction of a 1,3-diazide and phenylacetylene.

Our results also provide a convincing alternative explanation, shown in Scheme 6, for the fact that the Cu^{I}-catalysed reactions of certain 1,3-diazides with phenylacetylene give the bis(triazoles) as major products; in one case even when a reaction was carried out with a tenfold excess of a diazide.[11]

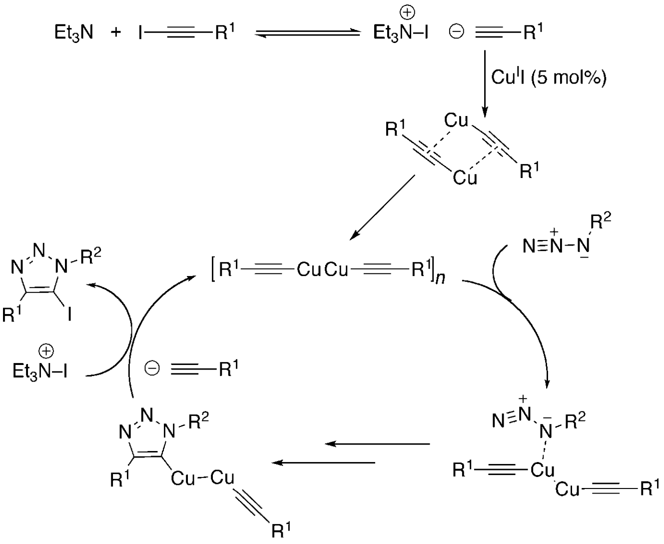
Ockham's razor, though not infallible,[32] suggested to us that, as a result of the efficiency with which alkynylcopper(I) catalysts such as **1** take part in CuAAC reactions; reactions of 1-iodoalkynes with azides should be investigated by using our polymeric alkynylcopper(I) ladderane catalysts. Two possible mechanisms have been suggested for the iodoalkyne–azide cycloaddition reactions.[16] Although it is not possible to prove a particular mechanism, experimental results can exclude potential mechanisms. Analysis of the results of the investigation carried out at the Scripp's institute[16] with particular emphasis on the use of a wide variety of amines, suggested that the nucleophilicity of the amine used could be of key importance and we concluded that tris(triazolylmethyl)amine derivatives are not only strong bases,[31] but also powerful nucleophiles. We allowed a mixture of iodophenylethyne (**11**) and benzyl azide to react in THF, with **1** and triethylamine as the catalyst system; the reaction gave a disappointing 20% yield of 1-benzyl-5-iodo-4-phenyltriazole. However, a similar reaction with 3-trifluoromethylbenzyl azide (**12**) in place of benzyl azide gave 1-(3-trifluoromethyl)benzyl-5-iodo-4-phenyltriazole (**13**) in 88% yield, as shown in Scheme 7. The yield of 1-(3-trifluorometh-



Scheme 7. Formation of 1-(3-trifluoromethyl)benzyl-5-iodo-4-phenyltriazole with a dinuclear Cu^{I} ladderane complex.

yl)benzyl-5-iodo-4-phenyltriazole (**13**) obtained in our reaction is the same as that reported earlier with copper(I) iodide, within experimental error.[16]

Although we cannot comment on the mechanistic suggestions reported for reactions of iodoalkynes with azides carried out with, for example, tris(triazolylmethyl)amines,[16] a minor modification of the mechanism shown in Scheme 5 is in accord with the results of our investigation of copper(I)-catalysed reactions by using 1-iodoalkynes and azides with ladderane catalyst **1**, and is shown in Scheme 8. Our results also have a bearing on recently reported reactions of alkynes and azides in the presence of stoichiometric amounts of copper(I) iodide.[33]



Scheme 8. Possible mechanism of the iodoalkyne–azide reaction with dinuclear Cu^I ladderane complexes.

A crossover reaction in which we allowed benzyl azide to compete for 1-iodophenylethyne (0.5 equiv) and 4-methoxyphenylpropargyl ether (0.5 equiv) in the presence of **1** resulted in the formation of four anticipated products, namely, 1-benzyl-4-phenyltriazole (**2**), 1-benzyl-4-(*p*-methoxyphenoxy)methyltriazole (**5**), 1-benzyl-5-iodo-4-phenyltriazole, and 1-benzyl-5-iodo-4-(*p*-methoxyphenoxymethyl)triazole (see the Supporting Information).

Conclusion

In summary, we have demonstrated that dinuclear alkynylcopper(I) ladderane complexes can be prepared by using a robust and simple protocol and that they are efficient catalysts in CuAAC reactions carried out under mild *t*BuOH/H_2O reaction conditions, as predicted by the Ahlquist–Fokin calculations. We established that the same copper(I) derivatives are formed during reactions by using the Sharpless–Fokin protocol and also that they function as catalysts in the related iodoalkyne–azide cycloaddition reactions.

Experimental Section

General experimental detail: All infrared spectra were obtained by using a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer; thin-film spectra were acquired by using sodium chloride plates. All ^1H and ^{13}C NMR spectra were measured at 400.13 and 100.62 MHz by using a Bruker DPX 400 MHz spectrometer or a Bruker Avance 400 MHz spectrometer. The solvent used for NMR spectroscopy was $CDCl_3$ unless stated otherwise, with TMS (tetramethylsilane) as the internal reference. Chemical shifts are given in parts per million (ppm) and J values are given in Hertz (Hz). GCMS analysis was performed by using a Fisons GC 8000 series (AS 800), with a 15 m × 0.25 mm DB-5 column and an electron-impact low-resolution mass spectrometer. Melting points were recorded by using a Stuart Scientific melting point apparatus (SMP3) and are uncorrected. Microanalyses were performed by using an Exeter Analytical CE-440 Elemental Analyser. All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored by using thin layer chromatography (TLC) on aluminium-backed plates with Merck Kiesel 60 F254 silica gel. TLC plates were visualised by using UV radiation at $\lambda = 254$ nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with conc. sulfuric acid), followed by charring where appropriate. Purification by column chromatography used Merck Kiesel 60H silica adsorbent. Reactions requiring anhydrous conditions were carried out by using flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Reaction solvents were obtained commercially dry, except for light petroleum (b.p. 40–60 °C), which was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium sulfate or chloride. Dichloromethane was distilled over calcium hydride. THF was distilled under a nitrogen atmosphere from the sodium/benzophenone ketyl radical. 1-Iodoalkynes were prepared by using the method described by Hein, Fokin and co-workers[16] XRD data were recorded by using a Bruker Avance powder defractometer operating with monochromated $Cu_{K\alpha 1}$ radiation over the 2θ range 5–60° with a 0.0147 2θ step. Mass spectra were recorded by using a Thermo Fisher Exactive with an ion max source and ESI probe fitted with a Advion triversa nanomate; the mass range was 20–2000 with a resolution of better than 100 000.

$Cu_2(OH)_3OAc{\cdot}H_2O$: $Cu(OAc)_2{\cdot}H_2O$ (4.00 g, 20.1 mmol) was dissolved in H_2O (200 mL) and stirred at RT, then NaOH (200 mL, 0.1 M) was added slowly with vigorous stirring. The reaction mixture was left to stir for 7 d, then centrifuged at 2000 rpm for 15 min. The aqueous phase was decanted and replaced with deionised water and the mixture was centrifuged for a further 15 min. The process was repeated with ethanol and finally dichloromethane to give the product as a pale green solid. The structure was then confirmed by XRD (below) and found to be monohydrated by combustion analysis (calcd (%) for $Cu_2(OH)_3OAc{\cdot}H_2O$ C 9.41, H 3.16; found: C 9.31, H 2.86).

Representative synthesis of the ladder polymers

*$[(CuCCPh)_2]_n$ (**1**)*: $Cu_2(OH)_3OAc{\cdot}H_2O$ (0.30 g, 1.17 mmol) was suspended in methanol (50 mL), then phenylacetylene (0.40 g, 3.92 mmol) was added and the reaction mixture was stirred at 32 °C for 48 h before being filtered and washed with dichloromethane. The yellow filter cake was dried and analysed by XRD and found to be **1** (0.193 g, 99 %). The filtrate was evaporated under reduced pressure to afford the Glaser product (1,4-diphenylbuta-1,3-diyne) as a colourless crystalline solid (0.009 g, 8 %).

1,4-Diphenylbuta-1,3-diyne:[34] ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.54$–7.52 (m, 2H), 7.38–7.26 ppm (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 132.5$, 129.2, 128.4, 121.8, 81.6, 73.9 ppm.

Formation of 1 by using the Sharpless–Fokin click reaction protocol: Phenyl acetylene (0.310 g, 3.0 mmol) was suspended in a 1:1 mixture of water and *tert*-butyl alcohol (12 mL) and sodium ascorbate (0.3 mmol, 300 mL of freshly prepared 1 M solution in water) was added, followed by copper(II) sulfate pentahydrate (7.5 mg, 0.03 mmol, in 100 mL of water). The heterogeneous mixture was stirred vigorously and turned brown and viscous. After ≈15 min, a yellow precipitate was formed. The reaction mixture was centrifuged at 2000 rpm for 15 min. The aqueous/*tert*-butanol phase was decanted, replaced with deionised water and centrifuged for a further 15 min. The process was then repeated by using ethanol and finally dichloromethane to afford the product as a yellow solid that was characterised by XRD to be ladder complex **1**.

Representative procedure for the synthesis of triazoles by using sodium ascorbate: 3-(4-methoxyphenoxy)prop-1-yne (486.0 mg, 3.0 mmol) and benzyl azide (399.0 mg, 3.0 mmol) were suspended in a 1:1 mixture of water and *tert*-butyl alcohol (12 mL). Sodium ascorbate (0.3 mmol, 300 μL of freshly prepared 1 M solution in water) was added, followed by 3-(4-methoxyphenoxy)prop-1-ynylcopper(I) (6.7 mg, 0.03 mmol). The heterogeneous mixture was stirred vigorously overnight, then diluted with water (50 mL), cooled in ice and the white precipitate collected by filtration. After washing the precipitate with cold water, it was dried under vacuum to afford triazole **4** as an off-white powder (0.77 g, 91 %).

Representative procedure for the synthesis of triazoles: 3-(4-methoxyphenoxy)prop-1-yne (486.0 mg, 3.0 mmol) and benzyl azide (399.0 mg, 3.0 mmol) were suspended in a 1:1 mixture of water and *tert*-butyl alcohol (12 mL). 3-(4-Methoxyphenoxy)prop-1-ynylcopper(I) (6.7 mg, 0.03 mmol) was added and the heterogeneous mixture stirred vigorously overnight. The reaction mixture was diluted with water (50 mL), cooled in ice and the white precipitate collected by filtration. After washing the precipitate with cold water, it was dried under vacuum to afford triazole **4** as an off-white powder (0.84 g, 98 %). M.p. 112.0–113.2 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 7.52 (s, 1 H), 7.35–7.37 (m, 3 H), 7.26–7.27 (m, 2 H), 6.89–6.91 (m, 2 H), 6.80–6.84 (m, 2 H), 5.53 (s, 2 H), 5.13 (s, 2 H), 3.76 ppm (s, 3 H); ^{13}C NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 154.2, 152.3, 144.9, 134.5, 129.2, 128.8, 128.1, 122.5, 115.9, 114.7, 62.9, 55.7, 54.2 ppm; UV (film): $\tilde{\nu}$ = 3054.3, 2986.1, 2305.8, 1506.4, 1265.1, 1230.7, 1040.0 cm^{-1}; HRMS: *m/z* calcd for $C_{17}H_{18}N_3O_2$: 296.1394 $[M+H]^+$; found: 296.1391; elemental analysis calcd (%) for $C_{17}H_{17}N_3O_2$: C 69.14, H 5.80, N 14.23; found: C 69.09, H 5.77, N 14.12.

Crossover experiment—Triazole (6)[35] prepared from 2-methyl-3-butyn-2-ol and benzyl azide: 2-Methyl-3-butyn-2-ol (252.0 mg, 3.0 mmol) and benzyl azide (399.0 mg, 3.0 mmol) were suspended in a 1:1 mixture of water and *tert*-butyl alcohol (12 mL). Sodium ascorbate (0.3 mmol, 300 μL of freshly prepared 1 M solution in water) was added, followed by 3-(4-methoxyphenoxy)prop-1-ynylcopper(I) (6.7 mg, 0.03 mmol). The heterogeneous mixture was stirred vigorously overnight. The reaction mixture was extracted with dichloromethane (2 × 20 mL), dried over MgSO$_4$, filtered and evaporated under reduced pressure to give **6** as colourless crystals (560.0 mg, 86 %). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 7.27–7.41 (m, 6 H), 5.49 (s, 2 H), 1.63 ppm (s, 6 H); ^{13}C NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 156.1, 134.6, 129.1, 128.8, 128.2, 119.1, 68.5, 54.2, 30.5 ppm.

Representative procedure for the synthesis of 5-iodotriazoles: Iodophenylacetylene (0.23 g, 1.00 mmol) and benzyl azide (0.13 g, 1.00 mmol) were dissolved in THF (5 mL). The solution was treated sequentially with **1** (8.2 mg, 0.05 mmol) and triethylamine (0.28 mL, 2.00 mmol) and then allowed to stir at RT for 15 h. After this time, the reaction was quenched by addition of aqueous NH$_4$OH (10 %, 1 mL). The volatile components were removed under reduced pressure, and the resulting residue was dissolved in dichloromethane, washed with water and dried (MgSO$_4$). Solvents were removed under reduced pressure to afford an off-white solid. Column chromatography (eluent: light petroleum/ethyl acetate (20:1)) afforded 1-benzyl-5-iodo-4-phenyltriazole[16] as a colourless solid (0.04 g, 20 %).

1-(3-Trfluoromethy)benzyl-5-iodo-4-phenyltriazole (13):[16] Compound **13** was prepared according to the representative procedure from 3-trifluoromethylbenzyl azide (0.20 g, 1.00 mmol), and obtained as a colourless solid (0.38 g, 88 %). ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 7.94 (d, J = 8.6 Hz, 2 H), 7.60–7.64 (m, 2 H), 7.40–7.53 (m, 5 H), 5.73 ppm (s, 2 H); ^{13}C NMR (400 MHz, CDCl$_3$, 25 °C, TMS): δ = 150.4, 135.3, 131.5, 131.2, 130.0, 129.6, 128.8, 128.6, 127.4, 125.5 (q, J = 3.7 Hz), 124.8 (q, J = 3.8 Hz), 122.4, 76.4, 53.8 ppm.

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