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Fine-Tunable Tris(triazolyl)methane Ligands for Copper(I)-Catalyzed Azide–Alkyne Cycloaddition Reactions

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Abstract: The preparation of a small library of modular tris(triazolyl)methane ligands for copper-catalyzed azide–alkyne cycloaddition (CuAAC) reactions is reported. The synthesis of the first generation ligand, tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol (**1a**), suitable for work in aqueous systems, is reported at the 50–100 mmol scale through a one-stage, environmentally benign procedure. One-stage procedures for the synthesis of tris(aryltriazolyl)methanol structures (**1b**, phenyl; **1c**, *para*-trifluoromethylphenyl; **1d**, *para*-methoxyphenyl) designed for electronic fine-tuning of catalytic properties, and of **1a**-derived ethers **2c** (OBn) and **2d** (OMe), designed for CuAAC reactions in organic solvents, are also reported. The complete set of ligands (**1a–d**, **2c–d**) has been tested in the reaction of phenylacetylene with benzyl azide in six different solvents (water, hexane, toluene, dichloromethane, tetrahydrofuran, and acetonitrile), and this has allowed the identification of **1b**, **1c** and **2c** as the ligands depicting the highest tolerance to changes in solvent polarity within the considered family. The comparative performance of ligands **1b–d** and **2c** in the cycloaddition of a small family of alkynes with benzyl azide in two very different reaction media (1:1 *t*-BuOH/H_2O and toluene) has been studied as a guide for catalyst selection in specific applications. The applicability of **1c** in CuAAC reactions involving functional substrates in toluene has been explored under thermal and microwave-accelerated (tandem azide formation plus CuAAC reaction) reaction conditions.

Keywords: alkynes; azides; click chemistry; copper; cycloaddition reactions

Introduction

In the short period of time following its discovery,[1,2] the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction has evolved into one of the most employed connective strategies in organic chemistry[3] and has found application in many different fields.[4]

Initial reaction conditions for CuAAC reactions involved the *in situ* reduction of a Cu(II) salt such as $CuSO_4$, used at rather high loading, with ascorbic acid to generate in the reaction media the catalytically active Cu(I) species.[2] However, it was later realized that polydentate nitrogen ligands were able to stabilize Cu(I) intermediates[5] and could also accelerate the catalytic process,[6] and this allowed the direct use of Cu(I) salts as catalysts in CuAAC reactions at highly reduced loadings. Tris(triazolylmethyl)amines **I**,[5a,6a,c,7] tetraamino ligands **II**,[8] N-heterocyclic carbenes **III**[9] (Figure 1), as well as various copper-coordinating species[10] have been found to be excellent ligands for this chemistry.

In this context, we have recently introduced tris(triazolyl)methanol **1a** (Figure 2) as an effective ligand for CuCl, and have shown that the corresponding neutral complex (**1a·CuCl**) is a very efficient catalyst for the azide–alkyne [3+2] cycloaddition reaction

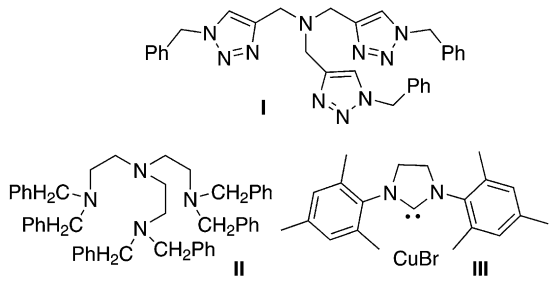

Figure 1. Cu(I) ligands for CuAAC reactions.

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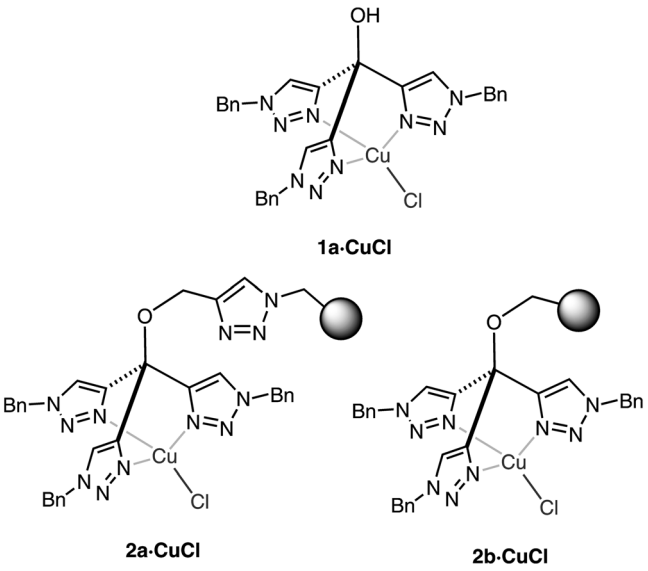


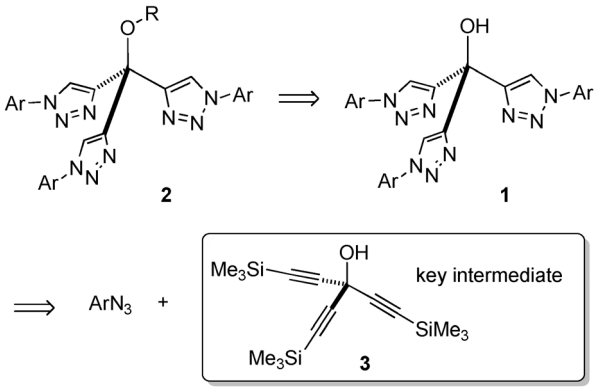
Figure 2. Homogeneous (**1a·CuCl**) and heterogenized (**2a·CuCl** and **2b·CuCl**) catalysts for CuAAC with the tris(triazolyl)methanol (TTM) structure.

in aqueous systems.[11] We have subsequently immobilized **1a** onto polystyrene resins by using different ligation methods, and have shown that the CuCl complexes of the functional resins **2a**, **2b** behave as highly active and recyclable catalysts for azide–alkyne cycloadditions in a variety of solvents.[12]

The structural characteristics of catalysts **1a·CuCl**, **2a·CuCl**,[12] and **2b·CuCl**[12] confer interesting properties to these materials. Thus, the three-point binding provided by the triazole units notably increases the stability of the CuCl complexes and allows their catalytic use at very low loadings even with substrates with high affinity for Cu, such as thioethers and primary and secondary amines.[11–13]

Tris(triazolyl)methanol (TTM) derivatives such as **1** and **2** are modularly constructed from a simple, readily available tris(alkynyl)methanol derivative **3**.[11] If the development of a general purpose catalyst library for CuAAC reactions based on this structure is considered, it can be readily envisioned that parameters such as solubility in aqueous or organic solvents can be controlled by simple etherification of the hydroxy group in **1** leading to **2**, while the use of diversely substituted aryl azides in the synthesis of the TTM structure can allow the modulation of electron density at the triazole unit and, consequently, at the copper atom in the corresponding CuCl complexes.[14]

To make this useful ligand fully available, we wish to report here a large-scale (50–100 mmol) preparation of **1a** through a one-stage process optimized to avoid potentially hazardous solvents or reagents, and not requiring any chromatographic separation. We also report the preparation of a small library of tris(triazolyl)methanol derivatives (**1b–d**, **2c**, **2d**) according to Scheme 1 and involving safe and scalable procedures. Derivatives **1b–d** are tris(aryltriazolyl)methanols designed to modulate electron density at a complexed Cu atom and to study the effect of this modulation on catalytic activity. Derivatives **2c**, **2d** are tris(aryltriazolyl)methanol ethers designed to expand the range of solvents where the corresponding CuCl complexes can be used in catalysis.



Scheme 1. Retrosynthetic analysis of TTM ligands **1** and **2**.

Results and Discussion

Implementation of a Scalable Procedure for the Preparation of 1a

The initially reported procedure for the preparation of **1a**[11] involved several chromatographic purifications and made use of the relatively expensive and potentially hazardous benzyl azide. In view of the interest in this ligand, whose activity and performance compare very favorably with those of highly priced, commercially available analogs, we aimed at developing an optimized procedure for the preparation of this material fulfilling the following requirements: (i) avoiding the isolation or purification of intermediates, (ii) using available reagents and environmentally convenient solvents, (iii) avoiding the use of benzyl azide, and (iv) avoiding the use of chromatography for the final purification of **1a**.

After extensive experimentation, the process represented in Scheme 2 was developed. In the optimized procedure, trimethylsilylacetylene (*ca.* 330 mmol) in anhydrous THF is converted to its Li salt by treatment with a solution of *n*-butyllithium in hexanes with strict temperature control ($\leq 15\,^{\circ}C$), and the generated acetylide is reacted with ethyl chloroformate (**4**, *ca.* 90 mmol; limiting reagent) in anhydrous THF, again with strict temperature control. The intermediate lithium salt arising from the double addition–elimination plus addition sequence (**3-Li**), obtained in THF solution does not need to be isolated for the

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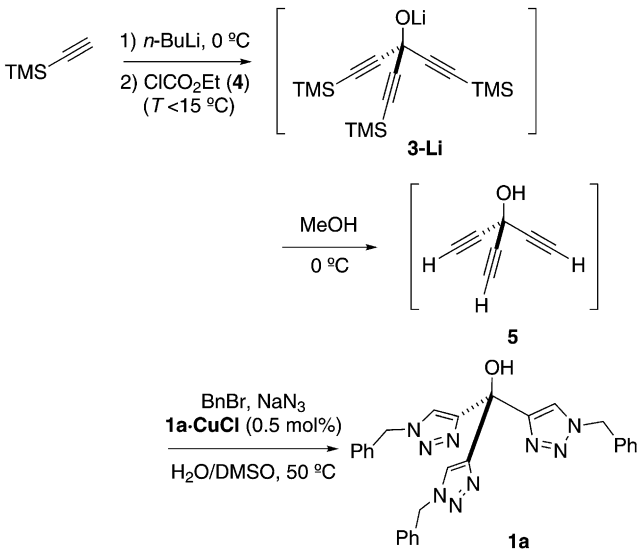


Scheme 2. Optimized procedure for the large-scale production of **1a**.

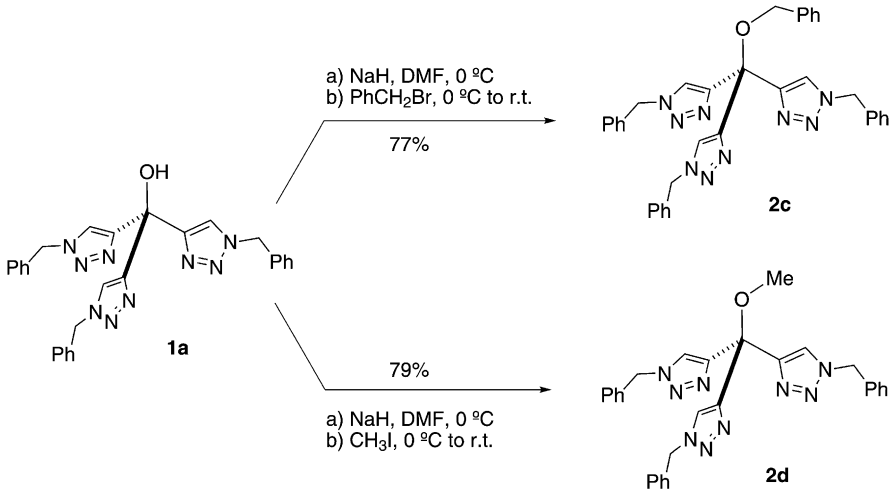
preparation of **1a**. If desired, however, the stable tris-(trimethylsilylethynyl)carbinol **3** can be easily isolated from this solution after neutralization and used as a convenient, advanced precursor for the synthesis of different TTM ligands.

Addition of excess MeOH to the THF solution of **3-Li** ($\leq$15 °C) followed by 2 h stirring at *ca.* 5 °C provokes complete protodesilylation of **3** and generates a light brown solution of **5**. Evaporation under vacuum to a final volume of 50 mL, followed by water addition (300 mL), evaporation of residual THF, and addition of a small volume of DMSO (10 mL) delivers a solution of **5** suitable for the triple CuAAC reaction leading to **1a**. This is performed by addition to the solution of **5** of benzyl bromide (310 mmol), sodium azide (330 mmol) and **1a·CuCl** (*ca.* 0.50 mmol). In this manner, benzyl azide reacts with **5** (or with its partially cycloadded derivatives) as it forms, and accumulation in the reaction media of this potentially hazardous reagent is avoided. Crude **1a**, which precipitates as the reaction proceeds, can be purified to a white powder by recrystallization from acetonitrile-ethyl acetate-cyclohexane (1:1:2). In this manner, 30 g of **1a** (64% yield) are obtained in a single batch, the whole process not involving a single purification by column chromatography. At this scale, the preparation of **1a** can be performed in a 1-L flask and involves the use of environmentally benign solvents and conventional reaction conditions. As we will see later in this update, the process can also be adapted for the one-pot preparation of aryl-substituted TTM ligands without isolation of the involved aryl azides.

Synthesis of Modular Tris(triazolyl)methane Derivatives

As we have already mentioned, the immobilization of **1a** on polystyrene matrices, using its hydroxy group as the anchoring point, allowed the preparation of complexes **2a·CuCl** and **2b·CuCl**, which performed as efficient and highly recyclable catalysts for CuAAC reactions in a variety of organic solvents. In view of this behavior, we decided to prepare simple monomeric ethers of **1a** in order to expand the use of their copper complexes to organic solvents covering a broad range of polarity. This can be of particular importance when the product triazoles need to be kept in solution as, for example, in processes involving multiple consecutive reactions.

The benzyl ether (**2c**) and the methyl ether (**2d**) were selected for this purpose and were readily prepared in high yield by simple etherification (Scheme 3).



Scheme 3. Etherification of **1a** leading to **2c**, **2d**.

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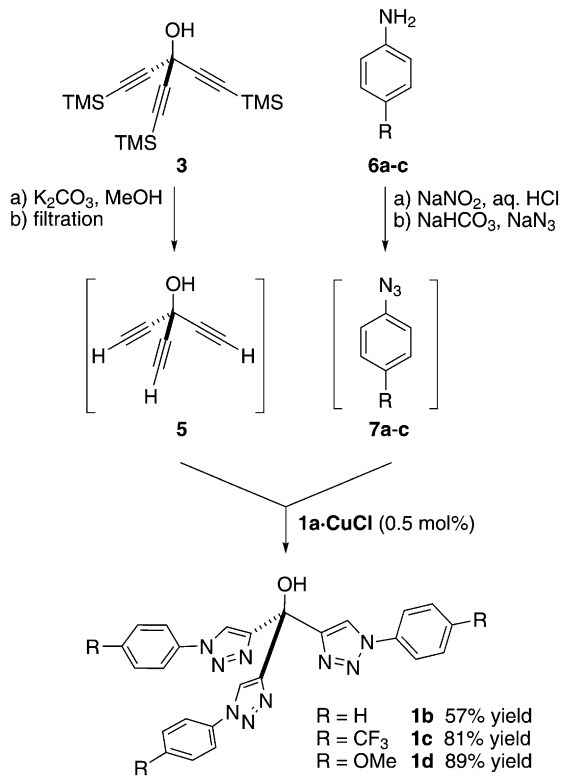


Scheme 4. One-stage preparation of **1b–d**.

The preparation of analogs of **1a** bearing aryl substituents at the triazole rings was also undertaken. In this manner, the electronic characteristics exerted by substituents at the aryl groups could be transmitted to the copper atom upon complexation, thus modulating the catalytic behavior of the complexes. As shown in Scheme 4, derivatives **1b** (R = H), **1c** (R = CF_3), and **1d** (R = OCH_3) were prepared for this purpose. The synthetic procedures for the preparation of **1b–d** were optimized in view of potential scale-up, and involved the use of benign solvents and reaction conditions, while avoiding manipulation and storage of aryl azides.

Tris(ethynyl)carbinol **5** was readily prepared in methanol solution from the stable and readily available alcohol **3** (see above) by protodesilylation with methanol in the presence of K_2CO_3 followed by filtration to remove solid materials. Aryl azides **7a–c**, in turn, were prepared in aqueous solution from the corresponding amines **6a–c** by treatment with HNO_2, neutralization, and reaction with sodium azide. Then, combination of the two solutions in the presence of **1a·CuCl** (0.5 mol%) and a small amount of DMSO (1% v/v) at room temperature led to the target TTM derivatives **1b–d** in 57–89% yield. Noteworthy, the preparation of these materials does not involve any chromatographic purification, and only a final recrystallization may be required.

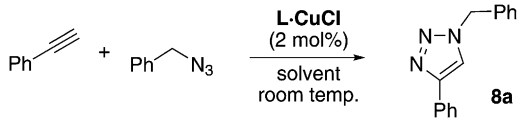
Performance of the CuCl Complexes of Modular Tris(triazolyl)methane Derivatives 1a–d and 2c, 2d in CuAAC Reactions

With the aim of determining the applicability of the prepared TTM ligands in CuAAC reactions, the cycloaddition between phenylacetylene and benzyl azide was first performed in different solvents in the presence of **1a–d** and **2c**, **2d**. The same amount of catalyst (2 mol%) was used in all cases and, for each particular solvent, the same reaction time was used with the whole set of ligands to facilitate comparison. The outcome of this study has been summarized in Table 1, where results for the optimal ligand/solvent combinations are and highlighted in boldface.

Several trends observed in this study deserve a comment. First, with the exception of **2d**, all the members of the considered family of catalysts perform very well in water (column 1), the reactions taking place in a short time with only 0.5 mol% catalyst loading. Second, and according to our expectations, ligands **2c** and **2d**, resulting from the etherification of the hydroxy group in **1a**, behave well in aprotic solvents of medium polarity (CH_2Cl_2, THF, CH_3CN). Third, among the tris(aryltriazolyl)methanols **1b–d**, both **1b** (R = H) and the electron-poor **1c** (R = CF_3) give high conversions in all the studied solvents at the specified reaction times; by contrast, ligand **1d** bearing the electron-rich 4-methoxyphenyl substituents originates a very poor catalyst in all solvents but in water.

Next, to determine if the catalytic behavior of the different ligands was correlated to the nature of the reactants, we decided to compare the performance of ligands **1b–d** and **2c** in four cycloadditions involving

Table 1. Comparative performance[a] of catalysts **1a–d** and **2c**, **2d** in the reaction of phenylacetylene with benzyl azide leading to **8a** in different solvents.



L	H_2O[b] 4 h	C_6H_{14} 6 h	$PhCH_3$ 6 h	CH_2Cl_2 6 h	THF 16 h	CH_3CN 16 h
1a	**98**	5	75	25	90	21
1b	**99**	**99**	**98**	**95**	**78**	**86**
1c	**82**	**99**[c]	**99**[d]	**99**	**80**	**50**
1d	**99**	14	2	22	3	10
2c	**99**	43	26	**98**	**92**	**96**
2d	**56**	27	69	**99**	**60**	**89**

[a] Conversion in [%].
[b] 0.5 mol% catalyst was used in this solvent.
[c] Conversion was 99% after 3 h and 73% after 1 h. With 1 mol% catalyst, conversion was 99% in 4 h. With 0.5 mol% catalyst, conversion was 73% after 4 h.
[d] Conversion was 95% after 3 h.

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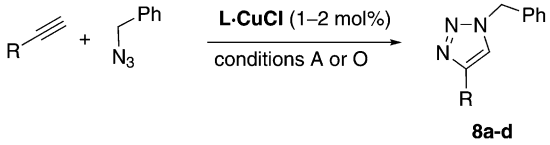
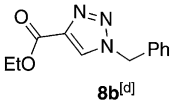
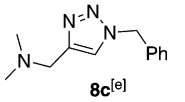
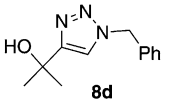
Table 2. Comparative performance[a] of ligands **1b**, **1c**, **1d**, and **2c** in the CuAAC reactions[b] of benzyl azide with representative alkynes.



8a-d

Product	**1b** A	O	**1c** A	O	**1d** A	O	**2c** A	O[g]
 **8a**[c]	**90**	99	99	**99**	64	4	80	21 (68)
 **8b**[d]	**99**	88	76	**85**	88	79	90	82 (75)
 **8c**[e]	**99**	63	99	**84**	79	69	88	99 (82)
 **8d**	**99**	63	95[f]	**72**[f]	66	59	73	67 (70)

[a] Isolated yields in [%].
[b] Aqueous conditions (A): (1:1) *t*-BuOH/H_2O, 4 h, room temperature; organic conditions (O): toluene, 4 h, room temperature.
[c] Reactions in conditions O performed with 2 mol% catalyst for 6 h.
[d] Reactions leading to this adduct performed with 2 mol% catalyst for 16 h.
[e] Reactions leading to this adduct in conditions O performed under argon.
[f] 2 mol% catalyst was used.
[g] Yields in parentheses correspond to reactions in dichloromethane.

in all cases benzyl azide and representative alkynes bearing different functionalities. The reactions were performed with 1 mol% catalyst loading, in two different solvent systems covering a wide range in polarity: 1:1 *tert*-butyl alcohol:water and toluene. Results of this study are summarized in Table 2, where results for optimal ligands and reaction conditions are highlighted in boldface.

To compare these results, it should be first kept in mind that one of the employed alkynes (i.e., 2-methyl-3-butyn-2-ol) is much less reactive with benzyl azide than the other three. When reactions in aqueous media are performed, **1b·CuCl** appears as the catalyst of choice. Thus, all four adducts are obtained in excellent yields with this catalyst and reaction conditions (column 1). For reactions in toluene, very good results are achieved with **1c·CuCl** (column 4), especially when the low reactivity of 2-methyl-3-butyn-2-ol is considered.

As we have already mentioned, **2c·CuCl** exhibits optimal catalytic conditions in organic solvents of medium polarity (see Table 1). To more properly assess the merits of this catalyst for the preparation of adducts **8a–d** in non-aqueous media, the reactions in column 8 of Table 2 were repeated in CH_2Cl_2 under otherwise identical conditions. Very gratifyingly, uniform yields (in parentheses) were obtained under these conditions for all four studied substrates. Thus, in preparative experiments a simple extension of reaction time will ensure very high yields of the corresponding adducts irrespective of the nature of the involved alkyne.

In view of the good performance exhibited by **1c·CuCl** for reactions in toluene leading to **8a–d** (mean yield: 85%), some additional experiments including especially challenging substrates, like primary amines, or problematic adducts, like those exhibiting good chelating characteristics for copper were performed in this solvent (Table 3). It is important to point out that CuAAC reactions involving these substrates usually fail when copper salts are used as metal sources, and this can be attributed to the formation of catalytically inactive Cu complexes involving either the reactants or the cycloadducts. According to the observed behavior of **1a·CuCl** in aqueous media, we reasoned that the efficient three-point metal binding in **1c·CuCl** would preserve its catalytic activity in toluene.

As it can be seen, **1c·CuCl** behaves as a very general and active catalyst for CuAAC reactions in this media. Proline derivatives depicting azido groups in different positions (entries 1–3) were efficiently converted into triazoles **8e–g**, which are advanced intermediates for organocatalytic prolines and pyrrolidines.[15] As already mentioned, functional group tolerance in the alkyne component is also very broad (entries 4–7) and alcohols, primary amines and esters lead to the corresponding adducts in high yield. In the same way, alkyl azides (entries 8–11) afford the corresponding cycloadducts in essentially quantitative yield. Very gratifyingly, 1,3,5-tris(azidomethyl)-2,4,6-triethylbenzene, an important precursor for supramolecular systems,[16] readily underwent triple CuAAC reactions mediated by **1c·CuCl** in toluene to afford the corresponding adducts **8p** and **8q** in very high yields (entries 12 and 13).

Finally, the use of **1c·CuCl** in tandem processes involving azide generation from an organyl bromide and sodium azide and subsequent CuAAC reaction is illustrated by the examples in Table 4. The reactions were performed in acetonitrile/water, at 100 °C under microwave irradiation in a remarkably short 40 min period.

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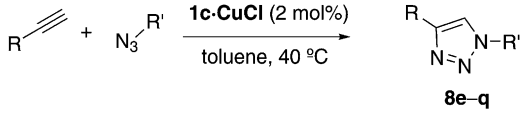
Table 3. CuAAC reactions mediated by **1c·CuCl** in toluene.



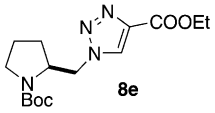
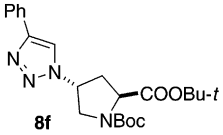
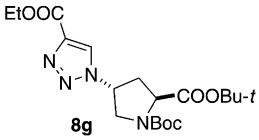
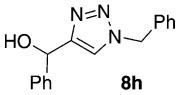
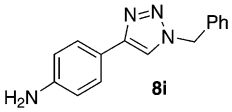
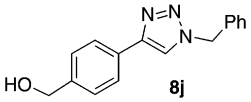
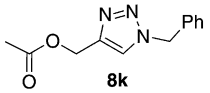
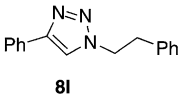
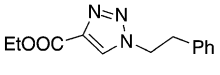
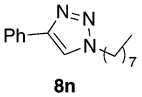
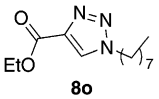
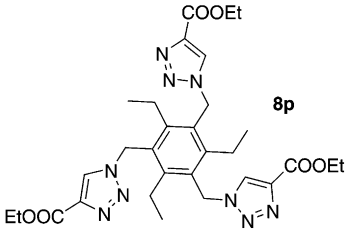
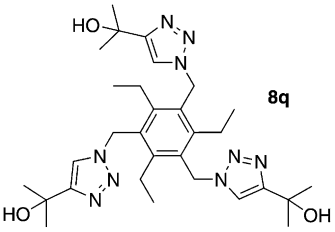
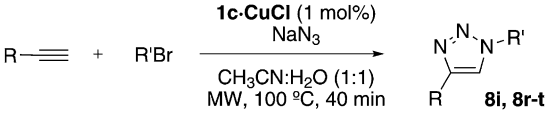
	Product	Time [h]	Yield [%][a]
1	 **8e**	2	95
2	 **8f**	22	99
3	 **8g**	3	99
4[b]	 **8h**	9	95
5	 **8i**	13	74
6	 **8j**	7	80
7[c]	 **8k**	10	99
8	 **8l**	22	99
9	 **8m**	2	93
10	 **8n**	20	99
11	 **8o**	2	99
12[d]	 **8p**	6	99

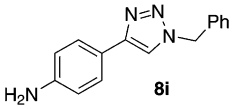
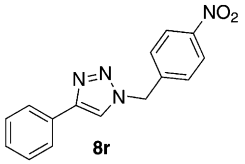
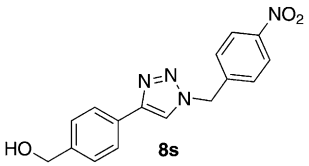
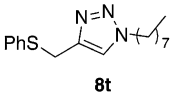
Table 3. (Continued)

	Product	Time [h]	Yield [%][a]
13[d]	 **8q**	24	80

[a] Isolated yields as mean value of two experiments.
[b] At room temperature.
[c] In *t*.BuOH-H_2O (1:1) at 40 °C.
[d] 2 mol% catalyst per CuAAC reaction.

Table 4. One-pot azide formation plus CuAAC reactions mediated by **1c·CuCl**.



Entry	Product	Yield [%][a]
1	 **8i**	55
2	 **8r**	98
3	 **8s**	99
4[b]	 **8t**	53

[a] Isolated yield as mean value of two experiments.
[b] Reaction time was 80 min.

Conclusions

The results presented in this study clearly show that modular tris(triazolyl)methanols (TTM) are among most useful ligands for copper-catalyzed azide–alkyne cycloaddition reactions. The three-point binding provided by these ligands efficiently stabilizes Cu(I) against oxidation or complexation with amino, hydroxy, and/or thioether groups present in either reactants or reaction products, likewise through favorable

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self-repair of the catalytic complex. This behavior not only extends catalyst life and allows very reduced catalyst loadings; it also allows its use with substrates (primary and secondary amines) where most catalysts for CuAAC reactions completely fail.

The first generation catalyst in this family, **1a·CuCl**, tolerates a wide range of functional groups on either the alkyne or the azide reactant, being particularly suitable for work in aqueous media. We believe that, with the fully optimized preparation of **1a** reported here, our catalyst constitutes a cost-efficient alternative to other Cu catalysts for similar purposes.[17]

The modification of the first generation catalyst, by simple etherification of the tertiary hydroxy group, provides catalytic species (**2c·CuCl** and **2d·CuCl**) suitable for work in organic solvents that behave particularly well in solvents of medium polarity.

The modular design of the TTM ligands has been exploited for the preparation of a small library of tris(aryltriazolyl)methanol derivatives **1b–d**. While the system involving a *para*-methoxy substituent in the aryl groups (**1d**) has proved to be a mediocre ligand, the parent tris(phenyltriazolyl) derivative (**1b**) and the one involving a *para*-trifluoromethyl substituent (**1c**) behave as very active ligands in a full range of solvents. In particular, **1c** tolerates a wide variety of functional groups on either the alkyne or the azide reactants, and appears as a convenient alternative to **1a** when work in non-aqueous solvents is mandatory.

Experimental Section

General Considerations

All reagents and solvents were used as received. For reactions requiring exclusion of oxygen and moisture, SPS quality THF and DMF were used. Unless otherwise stated, reactions were performed in oven-dried round-bottom flasks fitted with rubber septa and stirring bars, and reactions were conducted under a positive pressure of argon. Syringes or cannulae were used to transfer air- and moisture-sensitive liquids. All copper catalyzed azide–alkyne cycloaddition (CuAAC) reactions were performed in glass vials fitted with stirring bars without any precaution to exclude air and moisture. All flash chromatography purifications were carried out using 60 mesh silica gel and dry-packed columns. For thin layer chromatography (TLC) analysis, pre-coated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used, with UV light and/or phosphomolybdic acid (PMA) or basic aqueous potassium permanganate ($KMnO_4$) as developing agents. Solutions were concentrated under reduced pressure on rotatory evaporators at 30 °C. Nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz or 500 MHz for ^1H and at 100 MHz or 126 MHz for ^{13}C at room temperature. Chemical shifts (δ) are reported in parts per million (ppm) with respect to tetramethylsilane as internal standard, or to the corresponding solvent residual peak [$CDCl_3$: 7.28, 77.16; $(CD_3)_2SO$: 2.50, 39.52; CD_3OD: 3.31, 49.00; D_2O: 4.79 for proton and carbon, respectively]. The following abbreviations are used for the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br-s, broad signal. Melting points are all uncorrected. IR spectra were recorded on a FT-IR spectrometer operating in ATR mode.

Large-Scale Procedure for the Preparation of Tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol (1a)[11]

In a flame-dried, 1-L, three-neck, round-bottom flask, provided with magnetic stirrer, addition funnel and thermometer, a solution of trimethylsilylacetylene (47.0 mL, 332.6 mmol) in anhydrous THF (100 mL) is prepared. The solution is cooled with an ice-water bath, and stirred until the internal temperature is *ca.* 5 °C. Then, a solution of BuLi 2.5 M in hexanes (122.0 mL, 305.0 mmol) is slowly added to the solution from the addition funnel (exotherm!), controlling the addition rate in order to keep the internal temperature $\leq$15 °C. In this way, the addition is completed in *ca.* 1 h. The addition funnel is rinsed with fresh anhydrous THF (20 mL), which is also added to the reaction mixture. The solution is stirred in the ice-water bath (the internal temperature decreases to *ca.* 5 °C) for 1 h. Then, a solution of ethyl chloroformate (10.0 g, 92.2 mmol) in anhydrous THF (60 mL) is slowly added (exotherm!) through the addition funnel, controlling the addition rate so that the internal temperature is kept below 15 °C. In this way, the addition is completed in *ca.* 30 min. Afterwards, the addition funnel is rinsed with anhydrous THF (20 mL), which is also added to the reaction mixture. The reaction mixture is then allowed to warm slowly to room temperature (*ca.* 23 °C), and is stirred overnight. The solution takes a light brown color as the reaction proceeds. After 14 h at room temperature, TLC analysis of the light brown solution indicates the formation of tris(trimethylsilylethynyl)carbinol (eluent: cyclohexane/ethyl acetate 9:1; R_f: 0.37; stain: phosphomolybdic acid). Next, the reaction mixture is cooled with an ice-water bath until the internal temperature reaches *ca.* 5 °C, and then MeOH (100 mL) is slowly added through the addition funnel (exotherm!), controlling the addition rate in order to keep the internal temperature below 15 °C. This addition is completed in *ca.* 20 min. The reaction mixture is further stirred while cooling with the external ice-water bath (internal temperature stabilizes at *ca.* 5 °C) for 2 h. At this point, the reaction mixture has the aspect of a light brown solution. TLC analysis of this solution indicates formation of tris(ethynyl)carbinol (eluent: cyclohexane/ethyl acetate 9:1; R_f: 0.02; stain: phosphomolybdic acid). The mixture is concentrated under vacuum to a final volume of 50 mL, keeping the bath temperature at 30–35 °C. Water (300 mL) is then added, the solution is concentrated again under vacuum until only water distills, and the distillation is continued for 15–30 more minutes to ensure the removal of rests of organic solvent (bath temperature: 30–35 °C). Finally, enough water is added to adjust the volume of the solution to 300 mL. DMSO (10 mL) is then added, followed by benzyl bromide (37.0 mL, 312.0 mmol), sodium azide (21.5 g, 330.7 mmol) and **1a·CuCl** (0.277 g, 0.460 mmol, 0.5 mol%). The resulting mixture is warmed to 50 °C and stirred vigorously overnight at this temperature [**CAUTION: b*enzyl azide is formed under these conditions; benzyl azide may be explosive. Differential scanning calorimetry (DSC) of pure***

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benzyl azide shows an exothermic event starting at about 160°C, providing a sufficient safety margin]. After 14 h reaction, a brownish solid is abundantly formed, that tends to stick to the walls of the reactor. At this point, the progress of the reaction can be easily monitored by TLC, by taking a sample of the aqueous solution and extracting it with CH_2Cl_2. The absence of the spot corresponding to the starting tris(ethynyl)carbinol is indicative of reaction completion. The aqueous mother liquors are filtered, and all solids remaining in the reactor and in the filter are washed with water (2×100 mL, then 1×200 mL) [**CAUTION:** ***the aqueous phase should be disposed of with basic aqueous residues; addition of acid may generate hazardous and poisonous hydrazoic acid (HN_3) as a gas***]. The brownish solid recovered is partially dried on the filter by passing air through it and, while still wet, it is suspended in a mixture of acetonitrile (80 mL) and ethyl acetate (160 mL), warmed to reflux (internal temperature *ca.* 80 °C) and stirred at that temperature for 1 h. During this process, the solid almost completely dissolves. Cyclohexane (220 mL) is added slowly over 1 h while keeping the mixture under reflux, and then the mixture is cooled to room temperature (*ca.* 23 °C) over 3 h. The resulting slurry is aged overnight at room temperature. The white solid obtained is separated by filtration, then washed 3 times with a 1:1 mixture of ethyl acetate and cyclohexane (3×50 mL). The solid recovered is dried in an oven under vacuum overnight at 65 °C to afford **1a** as a white solid; yield: 29.8 g (64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (s, 3H), 7.32–7.18 (m, 15H), 5.76 (br-s, 1H), 5.39 (s, 3H); ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: δ = 151.4, 135.2, 127.9, 127.3, 127.2, 122.2, 67.1, 52.4.

Tris(1-phenyl-1*H*-1,2,3-triazol-4-yl)methanol (1b)

Concentrated aqueous hydrochloric acid solution [37% (v/v), 1.5 mL, 18 mmol] was added dropwise to a suspension of aniline (559 mg, 6.00 mmol) in water at 0 °C. After 15 min, a solution of sodium nitrite (621 mg, 9 mmol) in water (1 mL) was added *via* syringe. After 15 min, solid sodium bicarbonate was added until pH ~ 7, followed by addition of a solution of sodium azide (702 mg, 10.8 mmol) in water (1.7 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. In a simultaneous manner and in a separate flask, solid potassium carbonate (2.01 g, 14.5 mmol) was added to a solution of tris(trimethylsilylethynyl)methanol (**3**) (481 mg, 1.5 mmol) in methanol (5 mL) and the mixture was stirred at room temperature for 30 min. The solids were separated by filtration, and the solution was concentrated under reduced pressure to a final volume of *ca.* 3 mL. This solution was added to the mixture containing phenyl azide, followed by the addition of DMSO (0.15 mL) and **1a·CuCl** (9 mg, 0.015 mmol, 1 mol%), and the reaction mixture was stirred overnight at room temperature. After 14 h, a brown precipitate of **1b** was formed; it was separated by filtration and washed with cold diethyl ether (10 mL) to provide essentially pure **1b**. This material can be purified to analytical level by recrystallization from acetonitrile-water (1:2 mixture, 15 mL) to afford **1b** as a pale-yellow solid; yield: 394 mg (57%); mp 211–212 °C. ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.76 (s, 3H), 7.96 (d, 6H, J = 8.3 Hz), 7.60 (t, 6H, J = 7.9 Hz), 7.49 (t, 3H, J = 8.0 Hz), 7.16 (s, 1H); ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: δ = 152.6, 136.7, 129.9, 128.6, 121.4, 120.1, 68.0; FT-IR (neat): ν = 3304, 3138, 1597, 1548, 1466, 1235, 1042, 991, 889, 811, 750, 666 cm^{-1}; HR-MS (ESI-TOF): m/z = 484.1610 $[M+Na]^+$, calcd. for $C_{25}H_{19}N_9ONa$: 484.1614; elemental analysis: found (calcd. for $C_{25}H_{19}N_9O$): C 65.06 (65.07), H 4.27 (4.15), N 26.87 (27.32).

Tris(1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methanol (1c)

Following the above procedure for **1b** and starting from 4-(trifluoromethyl)aniline (967 mg, 6.00 mmol), **1c** was obtained as a pale-yellow solid; yield: 808 mg (81%); mp 240–241 °C. ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.96 (s, 3H), 8.25 (d, 6H, J = 8.5 Hz), 7.99 (d, 6H, J = 8.5 Hz), 7.32 (s, 1H); ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: δ = 152.7, 139.4, 128.6 (q, J = 32.42 Hz), 127.2 (q, J = 3.40 Hz), 124.3 (q, J = 274.05 Hz), 122.7, 121.9, 120.5, 67.4; ^{19}F NMR [376 MHz, $(CD_3)_2SO$]: δ −61.06; FT-IR (neat): ν = 3258, 1650, 1524,1323, 1161, 1126, 1069, 1044, 895, 840, 594 cm^{-1}; HR-MS (ESI-TOF): m/z = 688.1212 $[M+Na]^+$, calcd. for $C_{28}H_{16}F_9N_9ONa$: 688.1232.

Tris(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-methanol (1d)

Following the above procedure for **1b** and starting from 4-(methoxy)aniline (741 mg, 6.00 mmol), **1d** was obtained as a pale-yellow solid; yield: 736 mg (89%); mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 3H), 7.66 (d, 6H, J = 9.0 Hz), 7.02 (d, 6H, J = 9.0 Hz), 4.98 (s, 1H), 3.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 151.7, 130.4, 122.3, 120.9, 114.7, 68.1, 55.6; FT-IR (neat): ν = 3141, 2955, 2834, 1514, 1303, 1251, 1108, 1027, 888, 829, 796, 635, 530 cm^{-1}; HR-MS (ESI-TOF): m/z = 574.1927 $[M+Na]^+$, calcd. for $C_{28}H_{25}N_9O_4Na$: 574.1927.

4,4′,4″-[(Benzyloxy)methanetriyl]tris(1-benzyl-1*H*-1,2,3-triazole) (2c)

A solution of **1a** (503 mg, 1.0 mmol) in anhydrous DMF (2 mL) was added dropwise *via* cannula, under a positive pressure of argon, to a stirred suspension of sodium hydride (80 mg, 60% in oil, 2.0 mmol) in anhydrous DMF (2 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature (23 °C). After 2 h, the suspension became a clear solution, which was cooled to 0 °C and benzyl bromide (0.238 mL, 2.0 mmol) was added dropwise *via* syringe. The reaction mixture was allowed to warm to 23 °C and was stirred overnight. After 14 h, water (10 mL) was added dropwise and the mixture was extracted with dichloromethane (3×10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Residual DMF can be removed by dissolving the crude product in ethyl acetate-hexane (4:1, 50 mL) and washing with water (3×20 mL). Drying (anhydrous $MgSO_4$) and evaporation under reduced pressure affords crude **2c**, which is further purified by flash column chromatography (silica gel, ethyl acetate). The product was obtained as a white foam; yield: 0.456 g (77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (s, 3H), 7.32–7.28 (m, 9H), 7.24–7.19 (m, 6H), 7.19–7.11 (m, 5H), 5.44 (s, 6H), 4.41 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.0 138.1, 134.3, 128.9, 128.5, 127.9,

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127.7, 127.1, 124.4, 72.7, 66.5, 54.0; FT-IR (neat): $\nu = 3144$, 3064, 2934, 2871, 1496, 1453, 1226, 1130, 1040, 910, 889, 807, 734 cm^{-1}; HR-MS (ESI-TOF): $m/z = 616.2546$ $[M+Na]^+$, calcd. for $C_{35}H_{31}N_9ONa$: 616.2549.

4,4′,4″-(Methoxymethanetriyl)tris(1-benzyl-1*H*-1,2,3-triazole) (2d)

Following the above procedure for **2c** and using methyl iodide (0.124 mL, 2.0 mmol), **2d** was obtained as a white foam; yield: 0.408 g (79%); mp 127–129 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.80$ (s, 3H), 7.35–7.33 (m, 9H), 7.26–7.25 (m, 6H), 5.49 (s, 6H), 3.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 148.8$, 134.3, 129.1, 128.7, 128.1, 124.4, 72.8, 54.2, 52.1; FT-IR (neat): $\nu = 3141$, 2943, 1605, 1526, 1497, 1232, 1120, 1080, 856, 776 cm^{-1}; HR-MS (ESI-TOF): $m/z = 540.2229$ $[M+Na]^+$, calcd. for $C_{29}H_{27}N_9ONa$: 540.2236; elemental analysis: found (calcd. for $C_{29}H_{27}N_9O$): C 66.87 (67.30), H 5.18 (5.26), N 24.01 (24.36).

General Procedure for the Preparation of the Copper(I) Complexes of 1a–d and 2c, 2d

The ligand **L** (x mmol) (**L** = **1a–d**, **2c**, **2d**) and copper(I) chloride (1.05x mmol) in dioxane (10 mL $mmol^{-1}$ **L**) were stirred at 60 °C for 6 h. The solvent was then removed under reduced pressure, the green solid residue being redissolved in the minimal amount of dichloromethane (1–2 mL) and precipitated into hexane (20 mL) *via* dropwise addition of the dichloromethane solution. The solid material was collected by filtration and dried in a vacuum oven at 40 °C for 14 h to afford **L·CuCl**.

Tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol·CuCl (1a·CuCl)

Prepared according to the general procedure for complex formation using **1a** (0.504 g, 1.00 mmol) to afford the desired complex as a light green powder; yield: 0.588 g (98%). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.41$–7.07 (m, 18H), 5.92 (s, 6H); ^{13}C NMR (126 MHz, CD_3CN): $\delta = 131.6$, 131.2, 130.7, 129.9, 129.5, 101.0, 84.0; FT-IR (ATR, neat): $\nu = 3380$, 3111, 3062, 2949, 1718, 1584, 1432, 1142, 1077 cm^{-1};: HR-MS (ESI-TOF): $m/z = 566.1473$ $[M-Cl]^+$, calcd. for $C_{28}H_{25}N_9OCu$: 566.1473.

Tris(1-phenyl-1*H*-1,2,3-triazol-4-yl)methanol·CuCl (1b·CuCl)

Prepared according to the general procedure for complex formation using **1b** (0.232 g, 0.50 mmol) to afford the desired complex as a light green powder; yield: 0.233 g (83%). ^{13}C NMR (126 MHz, CD_3CN): $\delta = 135.1$, 131.0, 130.6, 129.9, 129.5, 126.8, 121.9; FT-IR (ATR, neat): $\nu = 3324$, 3136, 1597, 1552, 1465, 1237, 1039, 999, 892, 811, 752, 686 cm^{-1}; HR-MS (ESI-TOF): $m/z = 524.0997$ $[M-Cl]^+$, calcd. for $C_{25}H_{19}N_9OCu$: 524.1003.

Tris{1-[4-(trifluoromethyl)phenyl]-1*H*-1,2,3-triazol-4-yl}methanol·CuCl (1c·CuCl)

Prepared according to the general procedure for complex formation using **1c** (0.333 g, 0.50 mmol) to afford the desired complex as a green powder; yield: 0.330 g (86%). ^{13}C NMR (126 MHz, CD_3CN): $\delta = 133.5$, 131.1 (d, $J = 31.5$ Hz), 128.6, 126.6 (d, $J = 52.9$ Hz), 124.5 (d, $J = 49.0$ Hz), 122.4; FT-IR (ATR, neat): $\nu = 3085$, 1617, 1523, 1323, 1168, 1112, 1069, 1057, 843, 594, 469 cm^{-1}; HR-MS (ESI-TOF): $m/z = 728.0617$ $[M-Cl]^+$, calcd. for $C_{28}H_{16}F_9N_9OCu$: 728.0625.

Tris[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-methanol·CuCl (1d·CuCl)

Prepared according to the general procedure for complex formation using **1d** (0.276 g, 0.50 mmol) to afford the desired complex as a light green powder; yield: 0.257 g (79%). ^{13}C NMR (100 MHz, CD_3CN): $\delta = 161.4$, 134.7, 133.2, 131.6, 126.1, 123.8, 116.2, 56.8; FT-IR (ATR, neat): $\nu = 3353$, 3081, 2936, 2837, 1515, 1306, 1254, 1112, 1028, 830, 799, 613 cm^{-1}; HR-MS (ESI-TOF): $m/z = 614.1309$ $[M-Cl]^+$, calcd. for $C_{28}H_{25}N_9O_4Cu$: 614.1320.

4,4′,4″-[(Benzyloxy)methanetriyl]tris(1-benzyl-1*H*-1,2,3-triazole)·CuCl (2c·CuCl)

Prepared according to the general procedure for complex formation using **2c** (0.297 g, 0.50 mmol) to afford the desired complex as a light green powder; yield: 0.300 g (87%). FT-IR (ATR, neat): $\nu = 3448$, 3115, 3031, 2946, 2870, 1496, 1453, 1227, 1132, 1046, 980, 898, 807, 716 cm^{-1}; HR-MS (ESI-TOF): $m/z = 656.1928$ $[M-Cl]^+$, calcd. for $C_{35}H_{31}N_9OCu$: 656.1942.

4,4′,4″-(Methoxymethanetriyl)tris(1-benzyl-1*H*-1,2,3-triazole)·CuCl (2d·CuCl)

Prepared according to the general procedure for complex formation using **2d** (0.259 g, 0.50 mmol) to afford the desired complex as a light green powder; yield: 0.278 g (91%). FT-IR (ATR, neat): $\nu = 3135$, 2935, 1542, 1497, 1226, 1132, 1077, 893, 783, 717 cm^{-1}; HR-MS (ESI-TOF): $m/z = 580.1629$ $[M-Cl]^+$, calcd. for $C_{29}H_{27}N_9OCu$: 580.1629.

General Procedure for CuAAC Reactions

In a 3-mL vial, the specified amount of **L·CuCl** (**L** = **1a–d**, **2c**, **2d**) was added to a mixture of the reacting alkyne (1.05 mmol) and the corresponding azide (1.00 mmol) in the specified solvent (1 mL), and the mixture was stirred at 40 °C for the indicated times or until complete reaction. In reactions with complete conversion providing insoluble compounds, simple filtration afforded the desired CuAAC products with analytical purity. Otherwise, the reaction mixture was diluted with ethyl acetate (10 mL), and the resulting solution was washed with water (5 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. When required, the product was purified by flash column chromatography.

General Procedure for the Tandem Azide Formation and CuAAC Reactions under Microwave Irradiation

In a sealed microwave tube, sodium azide (91 mg, 1.40 mmol) was dissolved in water (1 mL). Acetonitrile (1 mL) was added as co-solvent, followed by the corresponding alkyl or benzyl bromide (1.20 mmol), the alkyne

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(1.0 mmol), and 1 mol% of catalyst **L·CuCl** (**L** = **1a–d**, **2c**, **2d**). The mixture was heated in the microwave reactor at 100 °C for 40 min (constant temperature mode, 5 min heating ramp, maximum power = 300 W, power max mode kept on; maximum allowed pressure = 300 PSI with stirring on). After cooling to room temperature, the reaction mixture was diluted with ethyl acetate. The solution was washed with water and brine, dried over $MgSO_4$, filtered, and volatiles removed under reduced pressure. If required, the triazole product was purified by flash chromatography on a short silicagel column, or by recrystallization.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (8a)[18]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.79 (m, 2H), 7.65 (s, 1H), 7.41–7.31 (m, 8H), 5.57 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.2, 134.7, 130.5, 129.1, 128.8, 128.14, 128.04, 125.7, 119.4, 54.2.

Ethyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate (8b)[19]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 2. ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.97 (s, 1H), 7.40–7.28 (m, 5H), 5.58 (s, 2H), 4.43–4.37 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.7, 140.6, 133.7, 129.3, 129.1, 128.2, 127.2, 61.3, 54.4, 14.3.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*,*N*-dimethylmethanamine (8c)[11]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 2. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (s, 1H), 7.37–7.36 (m, 3H), 7.27–7.25 (m, 2H), 5.51 (s, 2H), 3.58 (s, 2H), 2.25 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.7, 134.7, 129.1, 128.7, 128.1, 122.3 54.4, 54.1, 45.1.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (8d)[20]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 6H), 5.50 (s, 2H), 2.50 (s, 1H), 1.62 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 134.6, 129.1, 128.7, 128.1, 68.3, 54.2, 30.5 ppm.

(*S*)-Ethyl 1-[(1-*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-methyl-1*H*-1,2,3-triazole-4-carboxylate (8e)[21]

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.103 g, 1.05 mmol) and (*S*)-*tert*-butyl 2-(azidomethyl)pyrrolidine-1-carboxylate (0.226 g, 1 mmol) to afford the crude product that was further purified by flash column chromatography [silica gel, hexanes-ethyl acetate (3:1)] to give desired product as white solid; yield: 0.308 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (br s+s, 1H), 4.75–4.45 (m, 2H), 4.44–4.39 (m, 2H), 4.13 (br s, 1H), 3.43–3.09 (m, 2H), 1.97–1.73 (m, 3H), 1.50 (s, 9H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.6, 154.8, 140.3, 128.3,127.8*, 99.9, 80.5*, 80.1, 61.2, 57.0, 52.9*, 51.7, 47.0, 46.8*, 28.4, 28.2*, 23.3, 22.6*, 14.2 (*minor rotamer); elemental analysis: found (calcd. for $C_{15}H_{24}N_4O_4$): C 54.88 (55.54), H 7.07 (7.46), N 16.93 (17.27).

(2*S*,4*R*)-1,2-Di-*tert*-butyl 4-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)pyrrolidine-1,2-dicarboxylate (8f)

Prepared according to the general procedure for CuAAC reactions using ethynylbenzene (0.107 g, 1.05 mmol) and (2*S*,4*R*)-di-*tert*-butyl 4-azidopyrrolidine-1,2-dicarboxylate (0.312 g, 1 mmol) to afford the desired product as a white solid; yield: 0.410 g (0.99 mmol, 99%); mp 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.81 (m, 2H), 7.76 (s, 1H), 7.45–7.41 (m, 2H), 7.36–7.33 (m, 1H), 5.32–5.28 (m, 1H), 4.49–4.43 (m, 1H), 4.41–4.08 (m, 1H), 3.97–3.85 (m, 1H), 2.96–2.80 (m, 1H), 2.54–2.52 (m, 1H), 1.51 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.3, 153.5, 148.1, 130.3, 128.9, 128.3, 125.7, 118.2*, 118.0, 82.1*, 81.9, 80.9, 58.6*, 58.3, 57.8, 51.9*, 51.7, 36.7*, 35.7, 28.3*, 28.0 (*minor rotamer); FT-IR (ATR, neat): ν = 2978.1, 1725.4, 1691.1, 1401.3, 1367.1, 1257.7, 1130.4, 1040.7, 1006.4, 912.2, 767.7, 694.1, 512.9 cm^{-1}; HR-MS (ESI-TOF): m/z = 437.2151 $[M+Na]^+$, calcd. for $C_{22}H_{30}N_4O_4Na$: 437.2165; elemental analysis: found (calcd. for $C_{22}H_{30}N_4O_4$): C 63.55 (63.75), H 7.00 (7.30), N 13.66 (13.52); $[\alpha]_D^{25}$: −24.9 (*c* 0.1 in $CHCl_3$).

(2*S*,4*R*)-1,2-Di-*tert*-butyl 4-(4-Ethoxycarbonyl-1*H*-1,2,3-triazol-1-yl)pyrrolidine-1,2-dicarboxylate (8g)

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.103 g, 1.05 mmol) and (2*S*,4*R*)-di-*tert*-butyl 4-azidopyrrolidine-1,2-dicarboxylate (0.312 g, 1.0 mmol) to afford the desired product as a yellow oil; yield: 0.406 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 5.36–5.25 (m, 1H), 4.39–4.38 (m, 3H), 4.11–4.06 (m, 1H), 3.93–3.80 (m, 1H), 2.90–2.73 (m, 1H), 2.54–2.53 (m, 1H), 1.50–1.46 (m, 18H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.1, 160.5, 153.7*, 153.4, 140.6, 126.1, 125.9*, 82.2*, 82.1, 81.0, 61.4, 58.3, 58.1*, 51.8*, 51.6, 36.6*, 35.6, 28.2*, 28.0, 14.3 (*minor rotamer); FT-IR (neat): ν = 2976.9, 1698.6, 1476.8, 1453.3, 1206.2, 1147.1, 1042.4, 844.9, 754.7 cm^{-1}; HR-MS (ESI-TOF): m/z = 433.2063 $[M+Na]^+$, calcd. for $C_{19}H_{30}N_4O_6Na$: 433.2058; $[\alpha]_D^{25}$: −20.6 (*c* 0.1 in $CHCl_3$).

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanol (8h)[22]

Prepared according to the general procedure for CuAAC reactions using 1-phenylprop-2-yn-1-ol (0.139 g, 1.05 mmol) and benzyl azide (0.133 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.252 g (95%). ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 7.94 (s, 1H), 7.42–7.22 (m, 10H), 5.99 (d, J = 4.6 Hz, 1H), 5.83 (d, J = 4.6 Hz, 1H), 5.55 (s, 2H); ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: δ = 151.8, 144.0, 136.1, 128.7, 128.1, 128.0, 128.0, 127.0, 126.3, 122.1, 68.0, 52.7.

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)aniline (8i)[23]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 3 using 4-ethynylaniline (0.123 g, 1.05 mmol) and benzyl azide (0.133 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.185 g

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(74%). It was also prepared according to the general procedure for tandem azide formation and CuAAC reaction under microwave irradiation, as indicated in Table 4 using sodium azide (0.091 g, 1.4 mmol), benzyl bromide (0.205 g, 1.2 mmol) and 4-ethynylaniline (0.117 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.127 g (55%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 8.5$ Hz, 2H), 7.52 (s, 1H), 7.36–7.29 (m, 5H), 6.62 (d, $J = 8.6$ Hz, 2H), 5.58 (s, 2H), 3.76 (br-s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 134.9$, 129.1, 128.7, 128.0, 126.9, 121.1, 118.2, 115.2, 54.1.

[4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl]methanol (8j)[24]

Prepared according to the general procedure for CuAAC reactions using (4-ethynylphenyl)methanol (0.139 g, 1.05 mmol) and benzyl azide (0.133 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.212 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 8.5$ Hz, 2H), 7.65 (s, 1H), 7.40–7.31 (m, 7H), 5.57 (s, 2H), 4.70 (s, 2H), 1.90 (t, $J = 4.7$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta =$ 148.0, 140.9, 134.6, 129.8, 129.2, 128.8, 128.1, 127.4, 125.8, 119.4, 65.0, 54.2.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl Acetate (8k)[25]

Prepared according to the general procedure for CuAAC reactions using prop-2-yn-1-yl acetate (0.102 g, 1.05 mmol) and benzyl azide (0.133 g, 1.0 mmol) to afford the desired product as a colorless oil; yield: 0.229 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$ (s, 1H), 7.39–7.27 (m, 5H), 5.52 (s, 2H), 5.18 (s, 2H), 2.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 170.5$, 142.9, 134.2, 128.8, 128.5, 127.9, 123.4, 57.3, 53.9, 20.6.

1-Phenethyl-4-phenyl-1*H*-1,2,3-triazole (8l)[20]

Prepared according to the general procedure for CuAAC reactions using ethynylbenzene (0.107 g, 1.05 mmol) and (2-azidoethyl)benzene (0.147 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.247 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 8.5$ Hz, 2H), 7.46 (s, 1H), 7.42–7.27 (m, 6H), 7.14–7.13 (m, 2H), 4.63 (t, $J = 4.7$ Hz, 2H), 3.25 (t, $J = 4.6$ Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 147.5$, 137.1, 128.8, 128.7, 128.7, 128.1, 127.1, 125.7, 119.9, 51.7, 36.8.

Ethyl 1-Phenethyl-1*H*-1,2,3-triazole-4-carboxylate (8m)

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.103 g, 1.05 mmol) and (2-azidoethyl)benzene (0.147 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.228 g (93%); mp 64–66 °C ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$ (s, 1H), 7.32–7.18 (m, 3H), 7.09–7.08 (m, 2H), 4.64 (t, $J = 7.2$ Hz, 2H), 4.40 (q, $J =$ 6.0 Hz, 2H), 3.23 (t, $J = 7.2$ Hz, 2H), 1.39 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 160.6$, 139.9, 136.3, 128.8, 128.5, 127.6, 127.2, 61.1, 51.9, 36.4, 26.8, 14.2; FT-IR (ATR, neat): $\nu = 3084$, 2973, 1724, 1526, 1201, 1050, 1027, 695 cm^{-1}; HR-MS (ESI-TOF): $m/z = 246.1238$ $[M]^+$, calcd. for $C_{13}H_{16}N_3O_2$: 246.1237; elemental analysis: found (calcd. for $C_{13}H_{15}N_3O_2$): C 63.71 (63.66), H 6.15 (6.16), N 17.19 (17.12).

4-Octyl-1-phenyl-1*H*-1,2,3-triazole (8n)[26]

Prepared according to the general procedure for CuAAC reactions using ethynylbenzene (0.107 g, 1.05 mmol) and octyl azide (0.155 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.255 g (99%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.84$–7.83 (m, 2H), 7.74 (s, 1H), 7.42 (t, $J =$ 7.6 Hz, 2H), 7.33 (t, $J = 7.4$ Hz, 1H), 4.39 (t, $J = 7.3$ Hz, 2H), 2.01–1.90 (m, 2H), 1.35–1.26 (m, 10H), 0.87 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 147.7$, 130.7, 128.8, 128.0, 125.7, 119.3, 50.4, 31.7, 30.4, 29.0, 29.0, 26.5, 22.6, 14.0.

Ethyl 1-Octyl-1*H*-1,2,3-triazole-4-carboxylate (8o)[11]

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.103 g, 1.05 mmol) and octyl azide (0.155 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.251 g (99%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.07$ (s, 1H), 4.45–4.39 (m, 4H), 1.94–1.90 (m, 2H), 1.42 (t, $J = 7.1$, 3H), 1.31–1.28 (m, 10H), 0.88 (t, $J =$ 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 160.9$, 140.5, 127.2, 61.3, 50.7, 31.6, 30.1, 29.0, 28.8, 28.8, 26.3, 22.5, 14.3, 14.0.

Triethyl 1,1′,1″-[(2,4,6-Triethylbenzene-1,3,5-triyl)-tris(methylene)]tris(1*H*-1,2,3-triazole-4-carboxylate) (8p)

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.309 g, 3.15 mmol) and 1,3,5-tris(azidomethyl)-2,4,6-triethyl-benzene (0.327 g, 1.0 mmol) to afford the desired product as a thick oil; yield: 0.615 g (99%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.85$ (s, 3H), 5.73 (s, 6H), 4.40 (q, $J = 7.1$ Hz, 6H), 2.77 (q, $J = 7.5$ Hz, 6H), 1.39 (t, $J = 7.1$ Hz, 9H), 0.99 (t, $J = 7.5$ Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 160.5$, 146.8, 140.4, 129.9, 129.7, 61.4, 48.1, 23.6, 15.3, 14.2; FT-IR (neat): $\nu = 3127$, 2978, 1720, 1539, 1449, 1375, 1337, 1197, 1036, 840, 772 cm^{-1}; HR-MS (ESI-TOF): $m/z = 644.2919$ $[M+Na]^+$, calcd. for $C_{30}H_{39}N_9O_6Na$: 644.2916.

2,2′,2″-{1,1′,1″-[(2,4,6-Triethylbenzene-1,3,5-triyl)-tris(methylene)]tris(1*H*-1,2,3-triazole-4,1-diyl)}tris-(propan-2-ol) (8q)

Prepared according to the general procedure for CuAAC reactions using 2-methylbut-3-yn-2-ol (0.267 g, 3.15 mmol) and 1,3,5-tris(azidomethyl)-2,4,6-triethyl-benzene (0.327 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.463 g (80%); mp 208–209 °C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: $\delta = 7.66$ (s, 3H), 5.60 (s, 6H), 5.09 (s, 6H), 2.84 (q, $J = 7.4$ Hz, 6H), 1.41 (s, 18H), 0.76 (t, $J = 7.4$ Hz, 9H); ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: $\delta = 156.0$, 145.5, 130.1, 120.1, 67.2, 47.3, 30.7, 22.9, 14.8; FT-IR (ATR, neat): $\nu =$ 3328, 2973, 1456, 1370, 1166, 1041, 957 cm^{-1}; HR-MS (ESI-TOF): $m/z = 602.3554$ $[M+Na]^+$, calcd. for $C_{30}H_{45}N_9O_3Na$: 602.3538.

1-(4-Nitrobenzyl)-4-phenyl-1*H*-1,2,3-triazole (8r)[19]

Prepared according to the general procedure for tandem azide formation and CuAAC reaction under microwave irradiation, as indicated in Table 4, using sodium azide (0.091 g,

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1.4 mmol), 1-(bromomethyl)-4-nitrobenzene (0.258 g, 1.2 mmol) and ethynylbenzene (0.102 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.277 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.24$ (d, $J = 8.6$ Hz, 2H), 7.81 (d, $J = 7.2$ Hz, 2H), 7.74 (s, 1H), 7.47–7.32 (m, 4H), 7.34 (t, $J = 7.4$ Hz, 1H), 5.71 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 148.7$, 148.0, 141.7, 130.1, 128.9, 128.5, 128.4, 125.7, 124.3, 119.7, 53.2.

{4-[1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]phenyl}-methanol (8s)[11]

Prepared according to the general procedure for tandem azide formation and CuAAC reaction under microwave irradiation, as indicated in Table 4, using sodium azide (0.091 g, 1.4 mmol), 1-(bromomethyl)-4-nitrobenzene (0.258 g, 1.2 mmol) and (4-ethynylphenyl)methanol (0.132 g, 1.0 mmol) to afford the desired product as a white solid; yielöd: 0.307 g (99%). ^{1}H NMR (400 MHZ, CD_3OD): $\delta =$ 8.39 (s, 1H), 8.25 (d, $J = 8.6$ Hz, 2H), 7.79 (d, $J = 8$ Hz, 2H), 7.55 (d, $J = 8$ Hz, 2H), 7.42 (d, $J = 8$ Hz, 2H), 5.80 (s, 2H), 4.63 (s, 2H), 4.56 (s, 1H); ^{13}C NMR (126 MHz, CD_3OD): $\delta = 149.4$, 144.1,143.3, 130.6, 130.1, 128.6, 126.8, 125.2, 124.9, 122.7, 64.9, 54.1.

1-Octyl-4-[(phenylthio)methyl]-1*H*-1,2,3-triazole (8t)[11]

Prepared according to the general procedure for tandem azide formation and CuAAC reaction under microwave irradiation, as indicated in Table 4, using sodium azide (0.091 g, 1.4 mmol), octyl bromide (0.230 g, 1.2 mmol) and phenyl-(prop-2-yn-1-yl)sulfane (0.148 g, 1.0 mmol) to afford the desired product as a white solid; yield: 0.164 g (53%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$–7.25 (m, 5H), 7.20–7.17 (m, 1H), 4.28–4.24 (m, 4H), 1.84–1.81 (m, 2H), 1.25 (m, 10H), 0.88 (t, $J = 7.02$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 144.9$, 135.5, 129.5, 128.9, 126.4, 121.2, 99.9, 50.3, 31.7, 30.2, 29.0, 28.9, 28.9, 26.4, 22.6, 14.0.

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