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Copper Nanoparticles

Key Non-Metal Ingredients for Cu-catalyzed "Click" Reactions in Glycerol: Nanoparticles as Efficient Forwarders

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Abstract: The effect of long-alkyl-chain amines in CuI-assisted azide–alkyne cycloadditions of terminal alkynes with organic azides in glycerol and other environmentally benign solvents (water, ethanol) has been examined. The presence of these additives favors the in situ formation of Cu^{I}-based nanoparticles and results in an increase of the catalytic reactivity. In glycerol, liquid-phase transmission electron microscopy (TEM) analyses, enabled by the negligible vapor pressure of this solvent, proved that Cu^{I} nanoparticles are responsible for the observed catalytic activity. The wide variety of alkynes and azides of which this effect has been investigated (14 combinations) confirms the role played by these additives in Cu-catalyzed Huisgen cycloadditions.

Introduction

Copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions represent a successful method for the synthesis of 1,2,3-triazoles,[1] as indicated by the thousands of works published in this field,[2a] including enantioselective CuAAC transformations.[2b,c] This remarkable success is mainly due to the process versatility in terms of solvent compatibility, copper sources (salts, well-defined complexes, preformed nanoparticles, (un)-supported systems), functional group tolerance, and energy supplies (conventional heating, microwave activation) among others. However, this hands-on behavior leads to some concerns with regard to understanding ("who does what"), associated with the lack of conclusive studies in relation to CuAAC mechanism(s),[3] in particular for in situ generated systems using Cu^{I} starting materials. The most frequently used precursors, copper halides, are quite insoluble in the common organic solvents, especially CuI.[4] The presence of any additive (impurity) can improve the solubility of copper species in the medium, inducing then an increase of catalytic activity. In this context, organic bases play a decisive task, favoring both the coordination to metal (as Lewis bases) and the formation of active intermediates such as copper acetylides. Polydentate nitrogen-based ligands have been proved as particularly efficient copper partners, stabilizing Cu^{I} species[5] and enhancing the rate of CuAAC processes.[6] In this area, Cu^{I} complexes containing tris-(triazolyl)methane tripodal ligands, which are highly proficient in CuAAC reactions,[1f,7] represent an elegant approach to illustrate the role of Lewis bases (Figure 1). These ligands can efficiently stabilize catalytic precursors (**I**) and also intermediates acting as hemi-labile scaffolds (**II**), which generates vacant sites for the coordination of reagents.

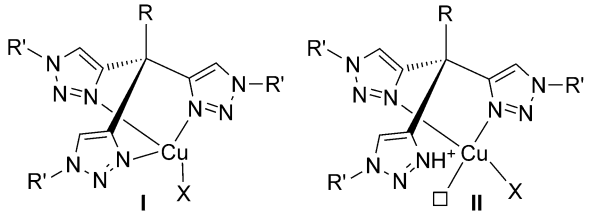

Figure 1. Tris(triazolyl)methane ligands for CuI-catalyzed AAC.[1f,7] Small square denotes vacant site on copper.

In agreement with these important, ancillary tasks, base-free catalytic CuAAC systems using Cu^{I} complexes as copper source are rare. To the best of our knowledge, only one recent publication by García-Alvarez and Vidal reports on a Cu^{I} system able to catalyze CuAAC reactions in glycerol in the absence of any added base.[8]

Following our work on the use of glycerol as a solvent in metal-catalyzed processes[9] and more recently in metal-free AAC for the synthesis of fully substituted 1,2,3-triazoles,[10] in which the activation of both alkynes and benzylazide by glycerol was proved, we planned to evaluate the activity of Cu^{I} salts towards click reactions in this solvent, with the aim of un-

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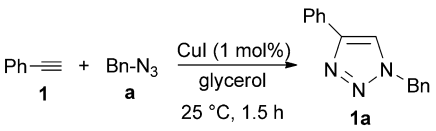
derstanding the role of added exogenous base in glycerol medium.

Results and Discussion

We selected the cycloaddition between phenylacetylene and benzyl azide as the benchmark reaction, using CuI as catalyst source in neat glycerol at room temperature (Scheme of Table 1). The reaction did not work at all at short reaction times (1.5 h), 84% conversion being achieved after 24 h (entry 1, Table 1). In the course of our research, the high efficiency of this methodology under exactly the same "base-free" reaction conditions was reported, triazole **1a** being isolated by these authors in 94% yield in short reaction times.[8] This serious discrepancy between independent runs of an easy-to-perform process, almost fulfilling the requirements in the Cornforth definition of an "ideal chemical process"[11] led us to think that some uncontrolled factor was operating. Given the practical importance of azide–alkyne cycloadditions, we decided to deeply characterize the different components involved in the process in an attempt to rationalize this behavior.[12] This analytical study showed that the success of the reaction depended on the quality (source) of BnN_3 (entries 2–4, Table 1) and that, rather surprisingly, high-purity samples of azide were unreactive. In fact only one commercially available lot of BnN_3 favored the cycloaddition (entry 2, Table 1).

Table 1. Azide–alkyne cycloaddition of phenylacetylene and benzyl azide in the presence of CuI.[a]

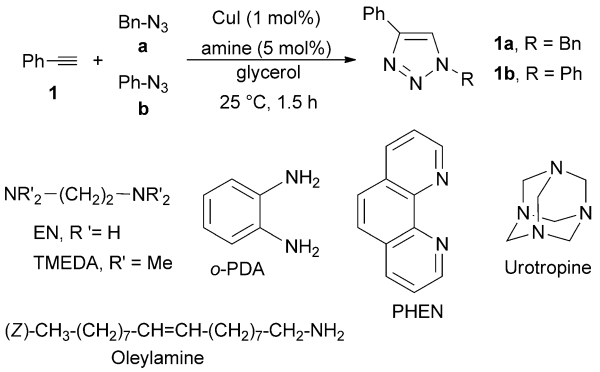


Entry	Bn-N_3 Source/Batch code[b]	Conv. (yield) [%][c]
1[d]	Home-made	< 5 *84 (69)*[e]
2	Alfa-Aesar/C25Z013[f]	100 (80)
3	Alfa-Aesar/AE040501	< 5
4	Aldrich/BCBL4667V	< 5

[a] Reaction conditions: CuI (1 mol%), benzyl azide (0.5 mmol), and phenylacetylene (0.5 mmol) in glycerol (0.5 mL) at 25 °C for 1.5 h. Triazole **1a** was not obtained in the absence of copper (18% conversion, < 5% yield for **1a**); [b] for certificates of analyses, see the Supporting Information; [c] determined by ^{1}H NMR analysis using 2-methoxynaphthalene as internal standard; conversions based on BnN_3; [d] for BnN_3 synthesis, see ref. [24]; [e] in italics, data after 24 h reaction; [f] data coming from two different commercial flasks.

We analyzed the "active" BnN_3 by GC-MS and NMR (Figures S1–S3 in the Supporting Information). In contrast to the other BnN_3 samples (Figures S4–S9 in the Supporting Information), this one was contaminated by some compounds that, according to MS, appeared to correspond to amines containing long alkyl chains. To test the possible catalytic effect of these impurities, we carried out the cycloaddition in the presence of amines using high purity, home-made BnN_3 (Table 2). We observed that when 5 mol% of amine with respect to benzyl azide was used, primary (entries 1–3), secondary (entry 4), and tertiary (entry 5) long-alkyl-chain-based mono-amines led to high yields of the corresponding 1,2,3-triazole, **1a**. For short-alkyl-chain derivatives, such as triethylamine or diisopropyle-

Table 2. Azide-alkyne cycloaddition of phenylacetylene and the corresponding azide in the presence of CuI and amine.[a,b]



Entry	Azide	Amine	Product, Conv. (yield) [%][b]
1	**a**	NH_2(octyl)	**1a**, 96 (93) *52 (44)*[c]
2	**a**	NH_2(undecyl)	**1a**, 96 (93)
3	**a**	Oleylamine	**1a**, 100 (> 99) *98 (94)*[c] Run 4: 100 (85)[d]
4	**a**	$NH(octyl)_2$	**1a**, 100 (96) *95 (88)*[c]
5	**a**	$N(octyl)_3$	**1a**, 96 (88) *97 (73)*[c]
6	**a**	NEt_3	**1a**, 28 (16)
7	**a**	$NEt(iPr)_2$	**1a**, 36 (6)
8	**a**	TOMACl	**1a**, 37 (19)
9[e]	**a**	Aliquat®336	**1a**, 20 (< 5)
10	**a**	TMEDA	**1a**, 83 (70)
11	**a**	EN	**1a**, 30 (12)
12	**a**	o-PDA	**1a**, 30 (10)
13	**a**	PHEN	**1a**, 15 (6)
14	**a**	Urotropine	**1a**, 20(< 5)
15	**a**	2,6-lutidine	**1a**, 34(26)
16	**b**	–	**1b**, < 5
17	**b**	NH_2(octyl)	**1b**, 100 (94) *39 (9)*[c]
18	**b**	Oleylamine	**1b**, 100 (98) *100 (87)*[c]
19	**b**	$NH(octyl)_2$	**1b**, 83 (89) *88 (87)*[c]
20	**b**	$N(octyl)_3$	**1b**, 88 (88) *100 (12)*[c]
21	**b**	NEt_3	**1b**, 10 (6)
22	**b**	TMEDA	**1b**, 70 (76)
23	**b**	EN	**1b**, 21 (19)
24	**b**	Urotropine	**1b**, < 5

[a] Reaction conditions: CuI (1 mol%), amine (5 mol%), benzyl or phenyl azide (0.5 mmol), and phenylacetylene (0.5 mmol) in glycerol (0.5 mL) at 25 °C for 1.5 h; [b] determined by ^{1}H NMR analysis using 2-methoxynaphthalene or 1,3,5-trimethoxybenzene as internal standard; conversions based on BnN_3; [c] in italics, conversion (yield) using 1 mol% of amine; [d] see Figure S10 in the Supporting Information for the recycling of the catalytic phase; [e] Aliquat® 336: Ammonium salts containing a mixture of C_8 and C_{10} alkyl chains with C_8 predominating.

thylamine, low yields were achieved (< 16%, entries 6 and 7, Table 2). When the amount of added amine decreased (1 mol%), the reaction also worked (entries 1 and 3–5), especially for oleylamine, dioctyl, and trioctyl amine (entries 3–5). Ammonium salts, such as trioctylmethylammonium chloride (TOMACl) and Aliquat®336 (ammonium salt containing a mixture of C8 and C10 alkyl chains, often used as a metal extraction reagent[13]), did not favor the cycloaddition (entries 8 and 9).

Dinitrogenated (EN = ethylenediamine; *o*-PDA = ortho-phenylenediamine and PHEN = phenantroline, entries 11–13, Table 2) and tetranitrogenated (urotropine, entry 14) ligands did not trigger a positive outcome (yields < 12%). TMEDA (tetramethylethylenediamine) was an exception to this behavior (70% yield, entry 10). The use of 2,6-lutidine, known by its performance in CuAAC in aqueous medium,[14] gave a very low yield (entry 15).

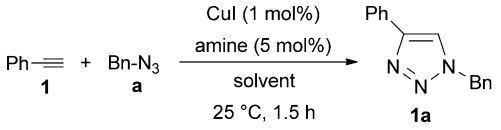
The same trend could be found when phenyl azide was used instead of benzyl azide (entries 16–24, Table 2): The system was inactive in the absence of an added amine (entry 16). However, high yields could be isolated in the presence of amines containing a long alkyl chain (up to 94%, entries 17–20). For "light" amines (entries 21–24,), only the CuI/TMEDA system was active, as previously observed with BnN_3 (entries 10 and 22, Table 2).

Furthermore, this "super" amine effect was examined in other polar solvents, such as water, ethanol, or 1,4-dioxane. Under the same conditions as described above, the behavior was comparable to that observed in glycerol. Without any additive or in the presence of NEt_3, low yields were obtained (< 13%, entries 1–6, Table 3). However, in the presence of dioctylamine (entries 7–9) or oleylamine (entries 10–12), the increase of catalytic activity was clearly apparent.

It is important to mention that the catalytic phase could be recycled up to four times without significant loss of efficiency (entry 3, Table 2; see Figure S10 in the Supporting Information), showing the ability of glycerol to immobilize the catalyst. The dramatic effect observed after the fourth run is undoubtedly related to the leaching of copper (more than 1000 ppm determined by ICP-MS).

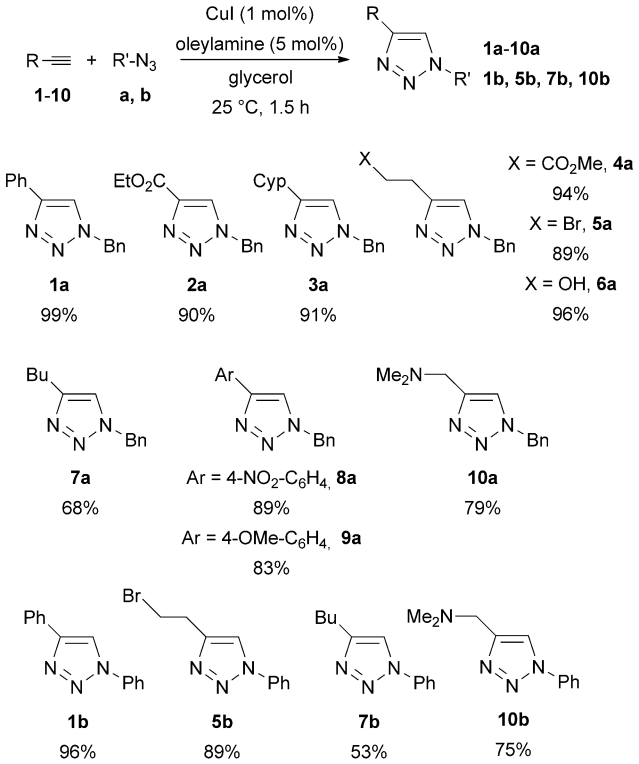
With these results in hand, a representative set of Cu-catalyzed azide–alkyne cycloadditions involving the use of different alkynes (**1**–**10**) and organo-azides (**a**, **b**) (Scheme 1) was carried out in the presence of oleylamine. The corresponding triazoles were obtained in high to quantitative yield. Even those triazoles bearing alkyl substituents at C-4 (**3a**, **7a**, **7b**) were obtained in moderate to high yields (53–91%). No transesterification reactions with glycerol were detected for alkynes containing ester groups (**2a**, **4a**). For selected triazoles, the reactions were also carried out in the absence of added amine, as control experiments. In all cases, low yields (< 25%, see Table S1 in the Supporting Information) were recorded even at longer times (up to 7 h). Unfortunately, this catalytic system, working under favorable conditions, was not active using internal alkynes, such as diphenylacetylene, methyl phenylpropiolate, or 1-iodo-2-phenylacetylene (Figure S11 in the Supporting Information).

Table 3. Azide-alkyne cycloaddition of phenylacetylene and benzyl azide in the presence of CuI and amine.[a]



Entry	Solvent	Amine	Conv. (yield) [%][b]
1	H_2O	–	22 (13)
2	EtOH	–	12 (< 5)
3	Dioxane	–	11 (< 5)
4	H_2O	NEt_3	15 (< 5)
5	EtOH	NEt_3	17 (< 5)
6	Dioxane	NEt_3	24 (11)
7	H_2O	$NH(octyl)_2$	100 (93)
8	EtOH	$NH(octyl)_2$	66 (48)
9	Dioxane	$NH(octyl)_2$	100 (99)
10	H_2O	Oleylamine	99 (94)
11	EtOH	Oleylamine	59 (48)
12	Dioxane	Oleylamine	94 (81)

[a] Reaction conditions: CuI (1 mol%), amine (5 mol%), benzyl azide (0.5 mmol), and phenylacetylene (0.5 mmol) in the appropriate solvent (0.5 mL) at 25 °C for 1.5 h; [b] determined by ^1H NMR analysis using 2-methoxynaphthalene or 1,3,5-trimethoxybenzene as internal standard; conversions based on BnN_3.



Scheme 1. Scope of azide-alkyne cycloaddition catalyzed by CuI/amine system in glycerol. Figures indicate isolated yields.

With the aim of understanding the observed reactivity, we analyzed the structural behavior of copper salts. From a coordination point of view, the CuI motif leads to a large variety of structures corresponding to both discrete molecular com-

plexes[15] and polymeric networks,[16] depending on the nature of the ligands involved and also the reaction conditions. This structural variety is especially remarkable when N-based ligands are involved,[17] in particular for diamines (EN, TMEDA, PHEN) and short-alkyl-chain tertiary amines (NEt_3, $NEtiPr_2$) like those used in this work.[18] Some of them give complex structures based on closed-cubane "Cu_4I_4" tetramers;[18a,19] we could prove this trend by the X-ray diffraction analysis of the Cu_4I_4-TMEDA system (Figures S12 and S13 in the Supporting Information).[20]

In contrast, long-alkyl-chain amines favor the stabilization of metal (and metal oxide) nanoparticles.[21] Presuming the formation of copper-based nanoclusters under our reaction conditions,[22] TEM analyses of CuI in glycerol and in the presence of different amines were carried out (Table S2 in the Supporting Information). Actually, the formation of well-dispersed nanoparticles was observed in the presence of long-alkyl-chain amines, including ammonium derivatives (Figure 2). HR-TEM and EDX analyses of a CuI/dioctylamine mixture in glycerol confirmed the Cu^I nature of the nanoparticles and the presence of the amine on the nanoparticle surface (Figure S14 in the Supporting Information). It is worth noting that ammonium salts such as TOMACl and Aliquat®336 did not lead to catalytically active systems, although the formation of well-dispersed nanoparticles was also observed. The lack of catalytic activity in these last cases is probably due to the very strong electrostatic interaction between the ionic ligands and the nanoparticles: As a result, Cu^I-based nanoparticles are tightly surrounded by anion/cation shells, and this leads to small and well-dispersed particles. However, this stabilizing interaction shields the surface of the nanoparticles and prevents the requisite approach of the reactants to the catalytic copper centers. In contrast, hemi-labile amine ligands, while still preventing particle agglomeration by steric shielding, can be easily detached, leading to free coordination sites on copper that are necessary for the reaction to proceed.[23]

Interestingly, the presence of additional ionic compounds in the reaction medium was shown to influence the course of the reaction as well. Thus, when an equimolar mixture of Aliquat®336 and a sodium salt (NaOAc or NaN_3) was added to the non-productive reaction mixture, the system turned active (Figure 3). TEM analyses of CuI in glycerol in the presence of both Aliquat®336 and sodium salt evidenced the formation of micelle-like arrangements, giving high local density of copper and therefore favoring the reactivity. This effect can especially be observed in the case of the mixture Aliquat®336/NaOAc, where cylindrical micelles were identified, containing the copper species at the surface (accessible to the reagents) and the more hydrophobic constituents (ammonium alkyl species) probably placed inside of these nano-objects. A similar trend could be observed using TOMACl/NaN_3 (Figure S15 in the Supporting Information). It is important to note that CuI/NaN_3 and CuI/NaOAc systems (in the absence of any nitrogen-based ligand) were not active. In addition, this reactivity behavior points to the feasibility of CuAAC by a one-pot three-component approach. Actually, with Bn-Br, NaN_3 and phenylacetylene as starting materials, **1a** was isolated in 90% yield (see Scheme S1 in the Supporting Information)

Correlating reactivity and structure, it seems that the formation of nanoparticles favors the catalytic process, which points to a beneficial (cooperative) effect between neighboring Cu^I centers for the activation of both azide and alkyne reactants during the cycloaddition, as already noted in our previous work involving the use of Cu_2O nanoparticles as catalytic precursors in glycerol medium.[9a]

In fact, for short-chain alkyl amines such as DIPEA (DIPEA = *N*,*N*-diisopropylethylamine), ethylenediamine, or urotropine, agglomerates similar to those observed for CuI in the absence of any additive were formed (Table S2 in the Supporting Information), affording inactive catalytic systems (Table 2). Only CuI/TMEDA led to the simultaneous formation of nanoparticles and agglomerates. As we have already mentioned, this system depicted high catalytic activity in azide–alkyne cycloadditions (entries 10 and 22, Table 2).

We were also interested in establishing the oxidation state of copper involved in the active species. For that, we reused the catalytic phase corresponding to the active CuI/dioctylamine system (after reaction between phenylacetylene and benzyl azide). TEM analysis after catalysis showed smaller nanoparticles than before (ca. 1.4 nm (after) vs. 2.1 nm (before); Table S2 in the Supporting Information); the catalytic phase was then much less active (33% in the second run versus 100% in the first one). HR-TEM coupled to an electronic diffraction analysis showed that particles after the first catalytic

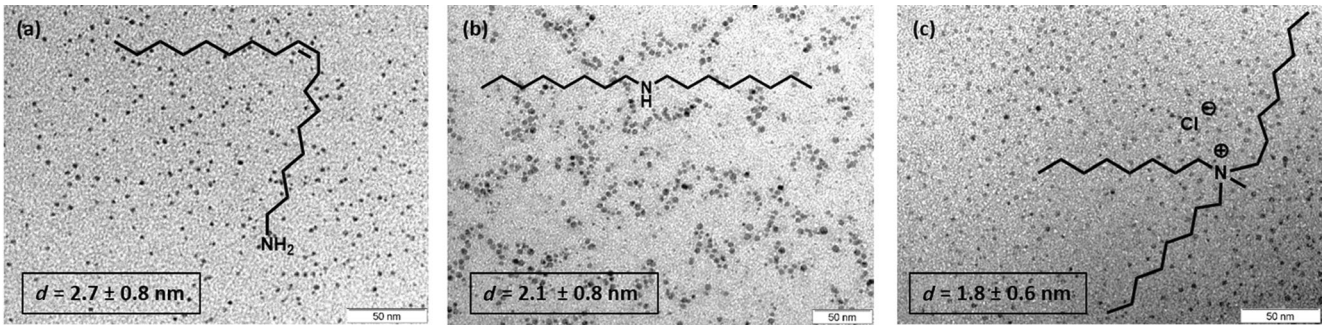


Figure 2. TEM images for CuI-based systems containing oleylamine (a), dioctylamine (b), and TOMACl (trioctylmethylammonium chloride) (c) in glycerol. Scale bars = 50 nm.

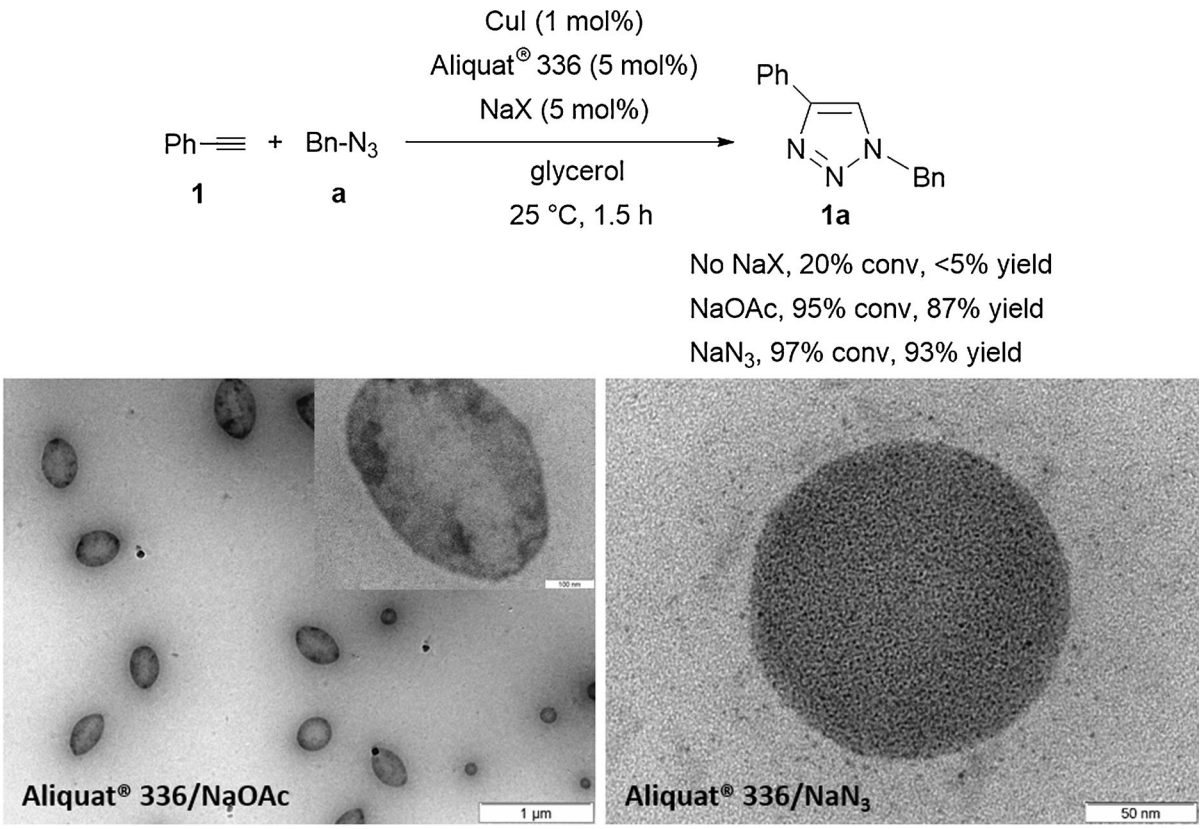


Figure 3. Effect of the salts in azide–alkyne cycloaddition. TEM images corresponding to the mixtures of CuI, Aliquat® 336, and NaX (1/5/5 ratio, respectively): NaOAc (left; scale bar = 1 μm, inset scale bar = 100 nm), including an inserted image of one of the cylindrical micelle-like objects; NaN_3 (right; scale bar = 50 nm).

run consisted of Cu^0 (Figure S16 in the Supporting Information). This indicated to us that the initially formed Cu^I-rich nanoparticles suffer reductive deactivation as a concomitant off-cycle of the CuAAC reaction. In contrast, the reutilization of the CuI/oleylamine system gave the same activity as for the first run (for both cases, nearly full conversion). HR-TEM/electronic diffraction analysis proved that in this case, nanoparticles were mainly formed by Cu^I after catalysis (Figure S17 in the Supporting Information). In addition, XPS analysis evidenced the absence of Cu^{II} species after reaction (absence of the corresponding strong satellites, see Figure S18 in the Supporting Information). These data point to Cu^I-based nanoparticles as being responsible for the observed reactivity.

Conclusions

In this work, we could prove the key role of "impurities" randomly present in commercial samples of benzyl azide. Its accurate analyses led us to identify them (long-alkyl chain amines) and to examine their impact on CuI-based catalytic systems applied in azide-alkyne cycloadditions in different solvents. As a practical result of this study, we have been able to establish that the addition of small amounts (5 mol%) of primary, secondary, or tertiary amines containing C_8, C_{11}, or C_{18} carbon chains (CuI/amine ratio = 1/1 or 1/5) secures the success in the synthesis of 1,4-disubstituted 1,2,3-triazoles under mild reaction conditions (low metal loading of 1 mol%, short time of 1.5 h, and room temperature), in environmentally benign glycerol. As a consequence, a warning should be made on experimental procedures for the CuAAC reaction in polar solvents not involving the use of appropriate amines: Their success or failure strongly depends on the presence/absence of amine-type impurities in the employed azide. The use of glycerol as a non-volatile solvent enabled the (HR)TEM analysis of solutions constituted by CuI and amine, before and after catalysis. It could be learned from these studies that CuI, in the presence of long-alkyl-chain amines in glycerol at room temperature, gives rise to the formation of small and well-dispersed Cu^I nanoparticles, in contrast with the agglomerates formed from either bulk CuI or mixtures of CuI with low-weight amines. It is important to mention that the presence of ammonium salts mainly containing C_8 chains (TOMACl, Aliquat® 336) did not provide an efficient catalytic system in spite of the formation of well-dispersed nanoparticles. This was almost certainly caused by the stabilization of CuI nanoparticles by electrostatic effect, thus blocking the access of reagents to the Cu^I centers. However, tuning the ionic species present in the reaction medium, the catalytic system turned active through the formation of organized systems.

Altogether, this study led us to establish a correlation between the in situ formation of Cu^{I} nanoparticles in glycerol and other polar solvents and their catalytic activity. These nano-objects, generated due to the presence of long-alkyl-chain amines, favor the activation of both reagents, alkyne and azide partners, by cooperative effect between neighboring Cu^{I} centers.

The inconsistencies found working under the "same" conditions induce the desire to understand and discover new issues for known reactions. The use of controlled-quality compounds (reagents, catalysts, solvents) permits a dramatic reduction of these effects, establishing reproducible and sustainable protocols.

Experimental Section

General procedure for the azide-alkyne cycloaddition

CuI (0.9 mg, 0.005 mmol) and the corresponding amine (0.005–0.25 mmol) were added to glycerol (0.5 mL) in a Schlenk tube equipped with a stirring bar under Ar atmosphere. The alkyne (0.5 mmol) and the azide (0.5 mmol, 67 mg for BnN_3[24] and 60 mg for PhN_3) were added consecutively to the reaction medium. The mixture was stirred at 25 °C for 1.5 h (or the stated time). The organic products were extracted from the catalytic mixture with dichloromethane (6×2 mL). The combined chlorinated organic layers were filtered through a Celite® pad and the resulting filtrate was concentrated under reduced pressure. The products were purified by chromatography (silica gel short column, eluent: cyclohexane/ethyl acetate) in order to determine the isolated yields of the corresponding triazoles.

Acknowledgements

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Keywords: azide–alkyne cycloaddition · copper · glycerol · long-chain amines · nanoparticles

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FULL PAPER

Copper Nanoparticles

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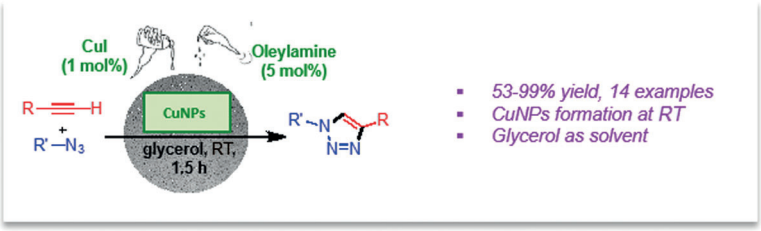
Key Non-Metal Ingredients for Cu-catalyzed "Click" Reactions in Glycerol: Nanoparticles as Efficient Forwarders



Super amines: The noteworthy reactivity observed in copper-catalyzed azide–alkyne cycloaddition reactions, with CuI in the presence of long-chain amines as starting catalytic materials, could be correlated to the in situ formation of Cu^{I} nanoparticles. These amines, acting as "super" ingredients, become crucial for accelerating the process, in particular in glycerol medium.