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Ramar Arun Kumar, Dhanaji Jawale, Emmanuel Oheix, Valérie Geertsen, Edmond Gravel, et al.. Tailor-made polydiacetylene micelles for the catalysis of 1,3-dipolar cycloadditions in water. *Advanced Synthesis and Catalysis*, 2020, 362 (20), pp.4425-4431. 10.1002/adsc.202000795 . cea-02907952

**HAL Id: cea-02907952**

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Submitted on 27 May 2024

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# Advanced Synthesis & Catalysis

## Accepted Article

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

**To be cited as:** *Adv. Synth. Catal.* 10.1002/adsc.202000795

**Link to VoR:** <https://doi.org/10.1002/adsc.202000795>

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

# Tailor-Made Polydiacetylene Micelles for the Catalysis of 1,3-Dipolar Cycloadditions in Water

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>.

**Abstract.** A colloidal catalyst was developed by complexation of copper chloride in polydiacetylene micelles. The latter were designed to accommodate and stabilize copper salts, by providing a suitable ligand environment. Micelles were valorized as nanoreactors for the promotion of the Huisgen cycloaddition reaction in water thanks to their central hydrophobic core which permitted not only aqueous dispersion, but also concentration of the reagents at the vicinity of the catalyst. The system was found to be active on a variety of substrates and efficiently operated under sustainable conditions.

**Keywords:** Micelle; Click; Polydiacetylene; Water solvent; Sustainable

## Introduction

The azide-alkyne 1,3-dipolar cycloaddition<sup>[1]</sup> is a widely used “click” reaction that has been exploited in various domains.<sup>[2]</sup> This [3 + 2] cycloaddition reaction has originally been disclosed by Huisgen who reported, in his 1963 paper, a thermally activated process.<sup>[3]</sup> More recent developments have led to the discovery of the copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC).<sup>[4]</sup> The CuAAC offers some key advantages over thermal activation such as milder operating conditions, improved regioselectivity, and better functional group tolerance. In the CuAAC, a Cu(I) catalyst is typically used in a mixture of aqueous and organic solvents. As copper salts can be toxic to biological systems and are difficult to remove from reaction mixtures, copper-free variants, involving cyclooctynes, have also emerged.<sup>[5]</sup> Yet, the strained cyclooctynes lack of chemoselectivity and are tricky to synthesize.<sup>[6]</sup>

With the aforementioned features in mind and as part of our longstanding interest in the development of catalytic systems,<sup>[7]</sup> we report here an original formulation of copper salts that were embedded in stable polydiacetylene micelles for the promotion of the [3 + 2] cycloaddition reaction in fully aqueous medium.<sup>[8]</sup>

Micelles are classically made from the self-assembly of amphiphilic molecules in water.<sup>[9]</sup> At a

concentration higher than the critical micelle concentration (CMC), amphiphiles aggregate into spherical structures with a hydrophilic outer layer, interfacing with water, and a central hydrophobic core. Micelles are valuable tools for organic transformations, including 1,3-dipolar cycloadditions, conducted in aqueous medium<sup>[10]</sup> as the lipophilic core of the micelles can accommodate hydrophobic molecules, allowing their dispersion and concentration.<sup>[11]</sup>

Our group previously developed stable polydiacetylene (PDA) micelles made from the self-assembly of diacetylene (DA) amphiphiles and photo-polymerized under UV irradiation.<sup>[12]</sup> The resulting PDA-micelles are robust and fully insensitive to dilution.<sup>[13]</sup>

The objective of the present work was accordingly to i) design amphiphilic diacetylene units capable of behaving as ligands for copper salts, ii) assemble stable polydiacetylene micelles containing copper, and iii) evaluate the hybrid micellar assembly as nanoreactor<sup>[14]</sup> for the catalysis of the 1,3-dipolar cycloaddition reaction in water. In addition, easy recovery/removal of the catalyst was anticipated.

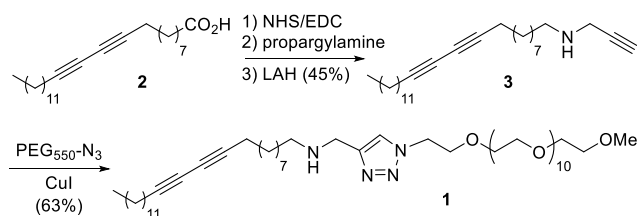
## Results and Discussion

The starting amphiphile **1** was designed in order to incorporate an amino-triazole unit in between the

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lipophilic diacetylene chain and the hydrophilic polyethyleneglycol (PEG) polar head. It has been previously demonstrated by others that amino-triazole motifs are capable of binding copper salts to provide stable complexes which were used for the catalysis of “click” reactions, in the presence of sodium ascorbate and in a binary mixture of solvents (H<sub>2</sub>O/EtOH).<sup>[15]</sup> The amino-triazole unit, incorporated in the structure of the amphiphile, should thus provide a suitable ligand environment to accommodate and stabilize copper salts within the micelle.<sup>[16]</sup>

Amphiphile **1** was readily synthesized in five steps, starting from commercially available pentacosadiynoic acid **2** which was first activated as a succinimidyl ester by reaction with *N*-hydroxysuccinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, Scheme 1). The activated ester was then reacted with propargyl amine, leading to an amide intermediate which was reduced with lithium aluminium hydride (LAH). The resulting secondary amine **3** was obtained in 45% yield, over three steps. The cycloaddition reaction of **3** with azido-terminated polyethylene glycol monomethyl ether (PEG<sub>550</sub>, MW = 550 Da), in the presence of CuI, led to the formation of the target amphiphile **1**, incorporating the copper-complexing amino-triazole unit, in 63% yield. The choice of small PEG<sub>550</sub> units as outer layer components of the micelle was governed by the fact that the moderate steric hindrance of short PEG chains should allow reagents to enter the central nanoreactor compartment.



**Scheme 1.** Synthesis of copper-complexing amphiphile **1**.

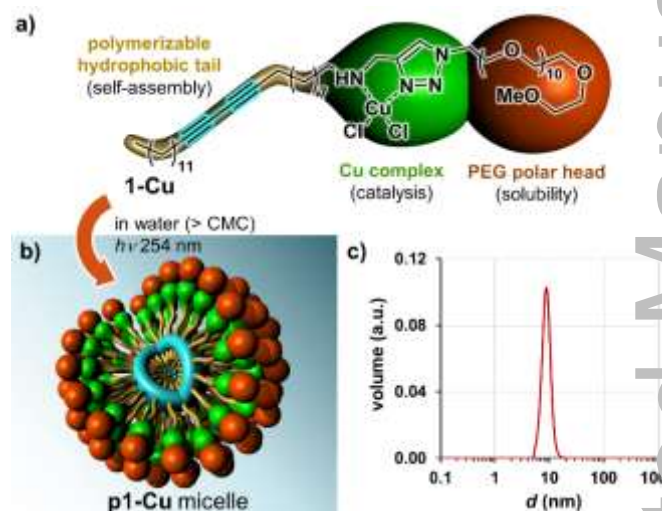
With amphiphile **1** in hands, we next induced the complexation of copper salts with the amino-triazole ligand by incubation of **1** with stoichiometric amounts of CuCl<sub>2</sub> in methanol. The mixture was stirred overnight at room temperature and the solvent was evaporated under vacuum to afford the **1-Cu** amphiphile complex, whose formation was confirmed by mass spectrometry (see Figure S1). It is to be noted that we also observed a green coloration of the amphiphile which was used as such in the next step.

The above amphiphile (**1-Cu**, Figure 1a) was then assembled into the corresponding micelle by dispersion in deionized water (10 mg of **1-Cu** per mL of H<sub>2</sub>O) using an ultrasonic probe. The micellar suspension was subjected to UV light irradiation at 254 nm for 3 h, under an inert argon atmosphere. UV irradiation triggered the topochemical polymerization of the diacetylene units, leading to the formation of

an ene-yne conjugated network in the core of each individual micelle and providing better cohesion to the assembly. The polymerized micellar solution was then dialyzed against water to remove unbound amphiphiles and free copper salts.

The resulting supramolecular assembly (**p1-Cu** micelle) is made of a central polymerized lipophilic core, an intermediate copper-complexed amino-triazole domain, and an outer hydrophilic layer made of PEG chains that provide full aqueous dispersion to the hybrid micelle (Figure 1b). Dynamic light scattering (DLS) analysis of the polymerized micelles incorporating copper chloride indicated a mean hydrodynamic diameter of *ca.* 9 nm (Figure 1c). Copper concentration of the aqueous micelle suspension was measured by inductively coupled plasma mass spectrometry (ICP-MS, [Cu] = 1 mM).

The micelle-encapsulated copper salts were then evaluated with regard to their catalytic properties, and more specifically their ability to promote the Huisgen 1,3-dipolar cycloaddition in aqueous medium, at room temperature.



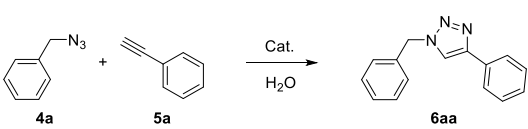
**Figure 1.** a) Structure of the **1-Cu** complex; b) Assembly and polymerization of amphiphilic **1-Cu** into **p1-Cu** micelles; c) Hydrodynamic diameter distribution obtained by DLS for **p1-Cu** micelles.

As opposed to previously reported procedures, in which a reductant such as sodium ascorbate was added to trigger Cu(II) to Cu(I) reduction,<sup>[17]</sup> we initially selected more straightforward conditions by exploiting the intrinsic one-electron transition from Cu(II) to Cu(I) observed in the course of the homocoupling of terminal alkynes. This process, known as the Glaser-Eglinton-Hay coupling,<sup>[18]</sup> affords dimeric alkynes together with reduced copper(I).<sup>[19]</sup> Cycloaddition reactions were thus run with an excess of the alkyne partner in order to promote *in situ* generation of the active Cu(I) species.

Benzyl azide (**4a**) and phenylacetylene (**5a**) were chosen as model substrates. Reaction conditions were

set by working in pure water, at room temperature, and under air atmosphere.

**Table 1.** Different conditions investigated for the Huisgen cycloaddition reaction.<sup>a</sup>



entry	Cu (mol%)	additive	yield (%) <sup>b</sup>
1	-	-	< 5 <sup>c</sup>
2	<b>p1-Cu</b> micelle (0.1)	-	25
3	<b>p1-Cu</b> micelle (0.2)	-	98
4	CuSO <sub>4</sub> (0.2)	Na ascorbate	48
5	CuCl <sub>2</sub> (0.2)	-	17
6	-	Cu-free <b>p1</b> micelle <sup>d</sup>	< 5 <sup>c</sup>

a) **4a** (0.1 mmol), **5a** (0.2 mmol), H<sub>2</sub>O (0.5 mL), Cu source, room temperature, 24 h. b) Yield of isolated product. c) <sup>1</sup>H-NMR yield. d) 1 mg mL<sup>-1</sup>.

When compounds **4a** and **5a** were reacted together in water in the absence of the Cu-loaded micelles, only trace amounts (< 5%) of **6aa** were detected after 24 h (Table 1, Entry 1). More gratifyingly, 0.1 mol% of the micelle-complexed copper (**p1-Cu** micelles) promoted partial cycloaddition to afford **6aa** in 25% yield (Entry 2). Yet, the best results were obtained by increasing the Cu loading to 0.2 mol% (Entry 3), as in this case we observed a nearly quantitative conversion after 24 h (98% yield), upon reaction with **p1-Cu** micelles (the participation of a Cu(I) species was demonstrated by spectrophotometric titration of the active copper, see ESI for details). These results have to be compared to those obtained under classical “click” reaction conditions, *e.g.* 0.2 mol% of copper(II) sulfate in combination with sodium ascorbate in excess, which only lead to half-conversion after 24 h (Entry 4). Additional control experiments included the use of CuCl<sub>2</sub> which poorly catalyzed the reaction (17%, Entry 5), and that of copper-free **p1** micelles which failed to activate any cycloaddition (Entry 6).

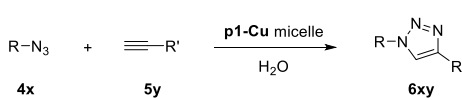
These results emphasize the key role played by the micellar system which not only acted as a colloidal stabilizer of copper salts but also as a nanoreactor which allowed aqueous dispersion of the reagents and their concentration at the vicinity of the active sites of the catalyst. Noteworthy, running the cycloaddition reaction on a larger scale (*e.g.*, 1.5 mmol) also provided a nearly quantitative yield of **6aa** (96%).

The scope of the **p1-Cu** micelle-catalyzed dipolar cycloaddition reaction was then studied on a variety of alkynes and azides under the optimized reaction conditions in water (Table 2). In addition to phenyl acetylene (**5a**, entry 1), benzyl azide also reacted with trifluoromethyl-substituted phenyl acetylenes **5b**

(entry 2) and **5c** (entry 3), and with aliphatic propargyl alcohol **5d** (entry 4). These substrates underwent smooth cycloaddition in nearly quantitative yields (95-96%) with the exception of **5d**, which afforded the desired cycloadduct **6ad** in a more moderate 65% yield.

In parallel, the compatibility of our system with an array of different azides was investigated, using phenylacetylene **5a** as the dipolarophile partner. The scrutinized 1,3-dipoles included electron-rich 2,4-dimethoxybenzyl azide **4b** (entry 5, 88%), electron-deficient *para*-cyanobenzyl azide **4c** (entry 6, 96%) and 4-(methoxycarbonyl)benzyl azide **4d** (entry 7, 70%).

**Table 2.** Scope of the **p1-Cu** micelle-catalyzed aqueous Huisgen reaction.<sup>a</sup>

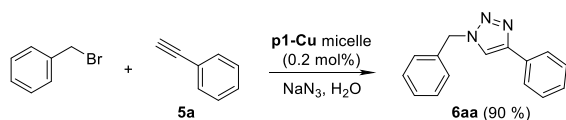


entry	azide <b>4</b>	alkyne <b>5</b>	Product <b>6</b> (yield %) <sup>b</sup>
1	<b>4a</b>	<b>5a</b>	<b>6aa</b> (98)
2	<b>4a</b>	<b>5b</b>	<b>6ab</b> (96)
3	<b>4a</b>	<b>5c</b>	<b>6ac</b> (95)
4	<b>4a</b>	<b>5d</b>	<b>6ad</b> (65)
5	<b>4b</b>	<b>5a</b>	<b>6ba</b> (88)
6	<b>4c</b>	<b>5a</b>	<b>6ca</b> (96)
7	<b>4d</b>	<b>5a</b>	<b>6da</b> (70)
8	<b>4e</b>	<b>5a</b>	<b>6ea</b> (86)
9	<b>4f</b>	<b>5a</b>	<b>6fa</b> (92)
10	<b>4g</b>	<b>5a</b>	<b>6ga</b> (75)
11	<b>4h</b>	<b>5a</b>	<b>6ha</b> (93)
12	<b>4i</b>	<b>5a</b>	<b>6ia</b> (97)

a) **4** (0.1 mmol), **5** (0.2 mmol), H<sub>2</sub>O (0.5 mL), **p1-Cu** micelles (0.2 mol%), room temperature, 24 h. b) Yield of isolated product.

The system was also equally efficient on two azido arene derivatives, *i.e.* plain azido benzene **4e** (entry 8, 86%) and 2-methoxyphenyl azide **4f** (entry 9, 92%), and on aliphatic 1,3-dipoles such as 3-azido propanol **4g** (entry 10, 75%), azido cyclohexane **4h** (entry 11, 93%), and sulfur-containing azide **4i** (entry 12, 97%). It is to be noted that, for all the above examples, the micelle-catalyzed [3 + 2] cycloaddition reaction proceeded in a regioselective fashion affording solely the 1,4-substituted triazole.

To further look into the applicability of our colloidal catalyst, the **p1-Cu** micelle was evaluated in the 1,3-cycloaddition reaction of a terminal alkyne with an *in situ* generated organic azide.<sup>[20]</sup> A tandem substitution-cycloaddition was planned, starting from benzyl bromide, sodium azide and phenyl acetylene in the presence of **p1-Cu** micelles (Scheme 2). We anticipated that benzyl azide could be produced *in situ* by nucleophilic displacement of the bromide atom and react with phenylacetylene. The one-pot sequence (R-X → R-N<sub>3</sub> → “click”) offers the advantage of a straightforward process without the need to pre-synthesize the azido partner. The three-component reaction was carried out at room temperature, under air, using 0.2 mol% of the **p1-Cu** micelle catalyst in water. We were pleased to observe that the expected cycloadduct **6aa** was produced in excellent 90% yield after 24 h.

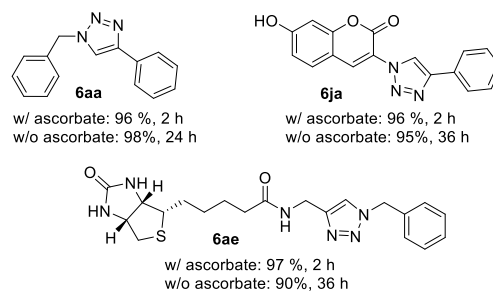


**Scheme 2.** One-pot reaction of benzyl bromide, sodium azide, and phenyl acetylene.

In order to establish the sustainability of the process, we assessed the recyclability of the **p1-Cu** micelle catalyst. To this end, four consecutive cycloaddition reactions of **4a** with **5a** were carried out using the same batch of **p1-Cu** catalyst which was recovered after each run and reused in subsequent reactions. After the reaction was completed, the aqueous phase was simply extracted with an organic solvent and the colloidal catalyst reused as such in water. It is to be noted that, although the system remained active, we observed a decrease in the catalytic performances, as the reactions gradually needed more time (from 24 to 48 h) to afford satisfactory yields of product **6aa** (Entries 1-4, Table S1). These results were surprising, as ICP-MS analysis of the organic extract after reaction did not reveal any copper that could have leached from the aqueous phase. Slow deactivation by aerobic oxidation of copper is thus likely responsible for the degradation of the catalyst performances. Yet, attempts to protect the catalyst

from oxidation by performing the different runs under an inert argon atmosphere were ineffective as reactions proceeded more sluggishly. As the performances of the catalyst were not fully satisfactory in terms of recycling, it was decided to investigate the potential benefit of adding sodium ascorbate to the reaction mixture.

Before being applied to the recycling of the catalyst, the ascorbate/**p1-Cu** micelle process was validated on selected substrates (Figure 2). Gratifyingly, the addition of sodium ascorbate (2 equiv.) to micellar copper proved beneficial to the click reaction as the cycloaddition of benzyl azide **4a** with phenylacetylene **5a** proceeded in 96% yield within 2 h and required only one equivalent of the alkyne partner. This result has to be compared to that of the initial procedure (ascorbate-free) which previously afforded triazole **6aa** in comparable yields, but in 24 h and using two equivalents of the alkyne. The same comment holds true for more complex substrates such as the coumarin-derived **6ja** (obtained by reaction of azido-coumarin **4j** with phenylacetylene **5a**) and biotin-based **6ae** (benzyl azide **4a** + biotin-alkyne **5e**) which were obtained in nearly quantitative yield by the ascorbate/**p1-Cu** micelle procedure after 2 h of reaction. As a comparison, 36 h are needed to produce coumarin **6ja** and biotin **6ae** in satisfactory yields by the initial ascorbate-free process. These results highlight the effectiveness of ascorbate-mediated click reactions but also the mildness of the operating conditions (w/ and w/o ascorbate) which permitted efficient access to rather sophisticated molecular structures in pure water.

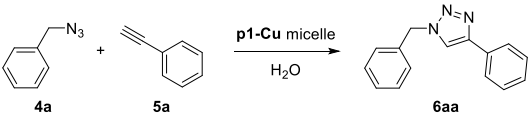


**Figure 2.** Examples of **p1-Cu** micelle-catalyzed reactions in the presence or absence of sodium ascorbate. Reaction conditions: 1) w/ ascorbate: azide (0.1 mmol), alkyne (0.1 mmol), sodium ascorbate (0.2 mmol), H<sub>2</sub>O (0.5 mL), Cu-micelle (0.2 mol% of Cu), room temp.; 2) w/o ascorbate: azide (0.1 mmol), alkyne (0.2 mmol), H<sub>2</sub>O (0.5 mL), Cu-micelle (0.2 mol% of Cu), room temp.

Recyclability of the **p1-Cu** catalyst was thereafter investigated under the new reaction conditions, involving sodium ascorbate (Table 3). Four consecutive cycloaddition reactions of benzyl azide **4a** with phenylacetylene **5a** were carried out using the same batch of the micellar **p1-Cu** catalyst which

was recovered after each run and reused in subsequent reactions. After completion of the reaction (2 h), the aqueous phase was extracted with an organic solvent and the colloidal catalyst reused in the presence of fresh reagents. Pleasingly, the catalyst remained active over the different cycles, giving access to triazole **6aa** in yields  $\geq 95\%$  (Entries 1-4). Interestingly, no decrease of the performances of the catalyst was observed in the case of the ascorbate-mediated reaction which supports the hypothesis that the observed deactivation under ascorbate-free conditions (Table S1) was likely due to *in situ* oxidation of the active copper species.

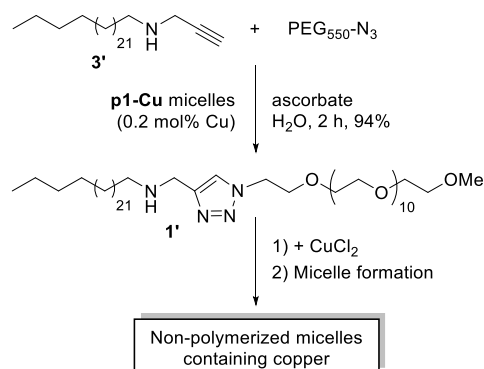
**Table 3.** Recycling experiment.<sup>a</sup>



entry	catalyst	yield (%) <sup>b</sup>
1	Fresh	98
2	1 <sup>st</sup> reuse	98
3	2 <sup>nd</sup> reuse	95
4	3 <sup>rd</sup> reuse	96

a) **4a** (0.1 mmol), **5a** (0.1 mmol), sodium ascorbate (0.2 mmol), H<sub>2</sub>O (0.5 mL), Cu-micelle (0.2 mol% of Cu), room temp., 2 h. b) Yield of isolated product.

We next investigated the influence of the polymerization of the micelles on the overall performances of the copper-based catalyst. For this purpose, non-polymerized micelles were assembled starting from the simple amphiphile **1** (yet incorporating the copper-complexing amino-triazole domain), and loaded with CuCl<sub>2</sub> (Scheme 3). Final copper concentration in the micellar stock solution was adjusted to 1 mM by addition of water. Interestingly, the non-polymerizable amphiphile **1'** was synthesized by a **p1-Cu**-catalyzed click reaction (in the presence of sodium ascorbate) between alkyne **3'** and azido-PEG<sub>550</sub>, in 94% yield (Scheme 3).



**Scheme 3.** Assembly of non-polymerized micelles containing copper.

With the non-polymerized copper-loaded micelles in hands, we next examined their ability to promote the Huisgen cycloaddition reaction on our model reaction between benzyl azide **4a** and phenylacetylene **5a**. Although the non-polymerized copper-loaded micelles catalyzed the click reaction under both conditions (w/ and w/o ascorbate), we observed a dramatic increase in the reaction times as 6 h were needed to produce triazole **6aa** in 91% yield in the presence of ascorbate (*vs* 2 h for the polymerized micelles) and 40 h were required to yield 87% of **6aa** without ascorbate (*vs* 24 h for the polymerized micelles). The lower catalytic activity of non-polymerized micelles could be ascribed to the intrinsic dynamic nature of the micelles in which an exchange of copper-containing amphiphiles between micellar arrays is taking place. This phenomenon reduces the time spent by the reagents in close contact with the metal centers in the environment of the nanoreactor, thus increasing reaction times. In addition, recycling of the catalyst could not be achieved in the case of the non-polymerized micelles, since work-up of the reaction using an organic solvent led to the extraction of most of the copper-bonded amphiphile, removing Cu from the aqueous phase which could no longer catalyze the click reaction. As a reminder, this phenomenon was not observed with the copper-loaded polymerized micelles that were retained in the aqueous phase, recycled, and reused.

Taken together our findings indicate that the Cu-complexing polymerized micelles behaved superiorly compared to their non-polymerized counterparts and that the addition of ascorbate enhances the performances of the system in terms of kinetics and recycling. In that sense, the **p1-Cu** micelles compare favorably to related micellar “click” catalysts which classically require either heating,<sup>[21]</sup> higher catalytic loadings,<sup>[22]</sup> or controlled atmosphere.<sup>[23]</sup>

## Conclusion

We have designed a new type of tailor-made copper-complexing micelles that were produced from the self-assembly, polymerization, and Cu-loading of amino-triazole-based amphiphiles. The stabilized hybrid micelles were valorized in the catalysis of the Huisgen cycloaddition, by taking advantage of the nanoreactor effect offered by the micellar environment, which allowed dispersion of the reagents and their concentration close to the active copper sites. The aqueous process efficiently operates on an array of substrates with low catalytic loadings, in the presence or absence of ascorbate and under sustainable conditions, as it neither requires heating nor controlled atmosphere. A one-pot sequence was

also developed for the 1,3-dipolar cycloaddition reaction by *in situ* generation of the organic azide from the corresponding halide. This further demonstrates the potential of the micellar system in terms of efficacy and the overall green aspect of the process.

## Experimental Section

**General Procedure for click reactions w/o ascorbate:** **p1-Cu** micelles (200  $\mu$ L of a 1 mM aqueous suspension, 0.2 mol%) were added to a suspension of aliphatic/aromatic azide (0.1 mmol) and terminal alkyne (0.2 mmol) in H<sub>2</sub>O (300  $\mu$ L). The reaction mixture was stirred at room temperature for 24 h, extracted with Et<sub>2</sub>O or AcOEt (3  $\times$  3 mL). The combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The crude product was purified by preparative thin layer chromatography.

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## Acknowledgements

R. A. K. thanks the Enhanced Eurotalents program for support. Dr. Annelaure Damont (CEA/DRF/DMTS/SPI) is gratefully acknowledged for helpful discussions. The "Service de Chimie Bioorganique et de Marquage" (SCBM) belongs to the Laboratory of Excellence in Research on Medication and Innovative Therapeutics (ANR-10-LABX-0033-LERMIT) and is a partner of NOMATEN, a Centre of Excellence in Multifunctional Materials for Industrial and Medical Applications.

## References

- [1] For reviews on recent advances in the field of azide-alkyne cycloadditions, see: a) E. Haldón, M. C. Nicasio and P. J. Pérez, *Org. Biomol. Chem.*, **2015**, *13*, 9528; b) M. S. Singh, S. Chowdhury, S. Koley, *Tetrahedron* **2016**, *72*, 5257.
- [2] a) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249; b) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905.
- [3] R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 565.
- [4] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.*, **2001**, *40*, 2004; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; c) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057; d) M. Meldal and C.W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952; e) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302.
- [5] a) J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli,

- C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16793; b) J. C. Jewetta, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272.
- [6] J. Dommerholt, F. P. J. T. Rutjes, F. L. van Delft, *Top. Curr. Chem.* **2016**, *374*, 16.
- [7] a) J. John, E. Gravel, A. Hagège, H. Li, T. Gacoin, E. Doris, *Angew. Chem. Int. Ed.* **2011**, *50*, 7533; b) D.V. Jawale, E. Gravel, E. Villemin, N. Shah, V. Geertsen, I. N. N. Namboothiri, E. Doris, *Chem. Commun.* **2014**, *50*, 15251; c) D. V. Jawale, E. Gravel, C. Boudet, N. Shah, V. Geertsen, H. Li, I. N. N. Namboothiri, E. Doris, *Chem. Commun.* **2015**, *51*, 1739; d) D. Clarisse, P. Prakash, V. Geertsen, F. Miserque, E. Gravel, E. Doris, *Green Chem.* **2017**, *19*, 3112; e) E. Gopi, E. Gravel; E. Doris, *Nanoscale Adv.* **2019**, *1*, 1181; f) M. D. Hoang, R. A. Kumar, D. A. Buisson, W. L. Ling, E. Gravel, E. Doris, *ChemCatChem* **2020**, *12*, 1156.
- [8] A. Adenot, E. B. Landstrom, F. Gallou, B. H. Lipshutz, *Green Chem.* **2017**, *19*, 2506.
- [9] a) D. Lombardo, M. A. Kiselev, S. Magazù, P. Calandra, *Adv. Cond. Matter Phys.* **2015**, 151683; b) J. Alliot, I. Theodorou, D. V. Nguyen, C. Forier, F. Ducongé, E. Gravel, E. Doris, *Nanoscale* **2019**, *11*, 9756; c) J. Alliot, I. Theodorou, F. Ducongé, E. Gravel, E. Doris, *Chem Commun.* **2019**, *55*, 14968.
- [10] a) G. La Sorella, G. Strukul, A. Scarso, *Green Chem.* **2015**, *17*, 644; b) B. H. Lipshutz, S. Ghorai, M. Cortes-Clerget, *Chem. Eur. J.* **2018**, *24*, 6672; c) D. K. Romney, F. H. Arnold, B. H. Lipshutz, C. J. Li, *J. Org. Chem.* **2018**, *83*, 7319.
- [11] a) D. Paprocki, A. Madej, D. Koszelewski, A. Brodzka, R. Ostaszewski, *Front. Chem.* **2018**, *6*, 502; b) S. Handa, B. Jin, P. P. Bora, Y. Wang, X. Zhang, F. Gallou, J. Reilly, B. H. Lipshutz, *ACS Catal.* **2019**, *9*, 2423; c) M. Cortes-Clerget, N. Akporji, J. Zhou, F. Gao, P. Guo, M. Parmentier, F. Gallou, J. Y. Berthon, B. H. Lipshutz, *Nat. Commun.* **2019**, *10*, 2169.
- [12] a) E. Gravel, J. Ogier, T. Arnauld, N. Mackiewicz, F. Ducongé, E. Doris, *Chem. Eur. J.* **2012**, *18*, 400; b) E. Gravel, B. Thézé, I. Jacques, P. Anilkuma, K. Gombert, F. Ducongé, E. Doris, *Nanoscale* **2013**, *5*, 1955; c) A. Doerflinger, N. N. Quang, E. Gravel, G. Pinna, M. Vandamme, F. Ducongé, E. Doris, *Chem. Commun.* **2018**, *54*, 3613; d) A. Doerflinger, N. N. Quang, E. Gravel, F. Ducongé, E. Doris, *Int. J. Pharm.* **2019**, *565*, 59; e) M. D. Hoang, M. Vandamme, G. Kratassiouk, G. Pinna, E. Gravel, E. Doris, *Nanoscale Adv.* **2019**, *1*, 4331; f) F. Costamagna, H. Hillaireau, J. Vergnaud, D. Clarisse, L. Jamgotchian, O. Loreau, S. Denis, E. Gravel, E. Doris, E. Fattal, *Nanoscale* **2020**, *12*, 2452.
- [13] a) N. Mackiewicz, E. Gravel, A. Garofalakis, J. Ogier, J. John, D. M. Dupont, K. Gombert, B. Tavitian, E. Doris, F. Ducongé, *Small* **2011**, *19*, 2786; b) I. Theodorou, P. Anilkumar, B. Lelandais, D. Clarisse, A. Doerflinger, E. Gravel, F. Ducongé, E. Doris, *Chem. Commun.* **2015**, *51*, 14937.



- [14] a) R. K. O'Reilly, *Phil. Trans. R. Soc. A* **2007**, *365*, 2863; b) P. Cotanda, N. Petzetakis, R. K. O'Reilly, *MRS Commun.* **2012**, *2*, 119.
- [15] a) D. Mendoza-Espinosa, G. E. Negrón-Silva, D. Angeles-Beltrán, A. Alvarez-Hernández, O. R. Suárez-Castillo, R. Santillan, *Dalton Trans.* **2014**, *43*, 7069. For examples of surfactants incorporating copper, see : b) S. Bhattacharya, K. Snehalatha, V. P. Kumar, *J. Org. Chem.* **2003**, *68*, 2741; c) F. Mancin, L. J. Prins, P. Pengo, L. Pasquato, P. Tecilla, P. Scrimin, *Molecules* **2016**, *21*, 1014; d) E. P. Zhiltsova, T. N. Pashirova, M. R. Ibatullina, S. S. Lukashenko, A. T. Gubaidullin, D. R. Islamov, O. N. Kataeva, M. P. Kutyreva, L. Y. Zakharova, *Phys. Chem. Chem. Phys.* **2018**, *20*, 12688.
- [16] P. S. Donnelly, S. D. Zanatta, S. C. Zammit, J. M. White, S. J. Williams, *Chem. Commun.* **2008**, 2459.
- [17] B. H. Lipshutz, Z. Boskovic, C. S. Crowe, V. K. Davis, H. C. Whittemore, D. A. Vosburg, A. G. Wenzel, *J. Chem. Educ.* **2013**, *90*, 1514.
- [18] W. Shi, A. Lei, *Tetrahedron Lett.* **2014**, *55*, 2763.
- [19] G. Zhang, H. Yi, G. Zhang, Y. Deng, R. Bai, H. Zhang, J. T. Miller, A. J. Kropf, E. E. Bunel, A. Lei, *J. Am. Chem. Soc.* **2014**, *136*, 16760.
- [20] a) P. X. Xiong, L. Cai, Y. Jiang, Q. Han, *ACS Sustainable Chem. Eng.* **2014**, *2*, 765; b) S. G. Agalave, S. G. Pharande, S. M. Gade, V. S. Pore, *Asian J. Org. Chem.* **2015**, *4*, 943; c) N. Mukherjee, S. Ahammed, S. Bhadra, B. C. Ranu, *Green Chem.* **2013**, *15*, 389; d) K. Chanda, S. Rej, M. H. Huang, *Chem. – Eur. J.* **2013**, *19*, 16036; e) P. Prakash, R. A. Kumar, F. Miserque, V. Geertsen, E. Gravel, E. Doris, *Chem. Commun.* **2018**, 54, 3644.
- [21] R. A. Youcef, M. Dos Santos, S. Roussel, J. P. Baltaze, N. Lubin-Germain, J. Uziel, *J. Org. Chem.* **2009**, *74*, 4318.
- [22] E. Tasca, G. La Sorella, L. Sporni, G. Strukul, A. Scarso, *Green Chem.* **2015**, *17*, 1414.
- [23] F. Xiang, B. Li, P. Zhao, J. Tan, Y. Yu, S. Zhang, *Adv. Synth. Catal.* **2019**, *361*, 5057.

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