Tetrahedron Letters 54 (2013) 1808–1812

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Are Cu(I)-mesoionic NHC carbenes associated with nitrogen additives the best Cu-carbene catalysts for the azide–alkyne click reaction in solution? A case study

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ARTICLE INFO

Article history:
Received 25 October 2012
Revised 10 January 2013
Accepted 14 January 2013
Available online 30 January 2013

Keywords:
N-heterocyclic carbene
Mesoionic carbene
Abnormal carbene
CuAAC
Click Chemistry

ABSTRACT

Copper(I)-catalyzed azide alkyne cycloaddition is now a widely used tool for the synthesis of elaborated compounds. Until now, few stable and efficient copper(I) catalysts are available despite the limitations inherent to approaches employing the in situ reduction of a Cu^{II} species to deliver the catalytic system. We report that the combination of a copper(I)-mesoionic N-heterocyclic carbene (MIC) with a phenanthroline derivative generates a highly active catalyst, functioning in aqueous alcoholic solvent, without the intervention of a reducing agent. This catalytic system surpasses related 'normal' N-heterocyclic carbene-based systems in their efficiency.

'Click chemistry' is defined as a paradigm for organic synthesis that invokes only simple, high-yielding, and easily workable transformations.[1] This has facilitated an extraordinary increase in the number and variety of molecules available for coordination and organometallic chemistry (ligand design, sensing studies), magnetic switching, supramolecular chemistry, therapeutics, biology, materials science, and catalysis.[2] Among 'click' reactions, the copper(I)-catalyzed azide alkyne cycloaddition (CuAAC)—a catalytic version of the Huisgen cycloaddition—has received unrivalled attention.[3] The most popular CuAAC catalytic systems consist of a combination of copper(II) and nitrogen-based ligands (TBTA, THPTA, bathophenanthroline...) in the presence of a sacrificial reducing reagent (ascorbic acid or TCEP [tris(2-carboxyethyl)-phosphane]) to obtain the active copper(I) species (Scheme 1).[4]

Alternatively, well-defined stable copper(I) complexes including N-, P-, S-, and C-based ligands can be employed. Therefore a pre-reduction step is not required, which constitutes an obvious advantage (Scheme 2).[5,6]

Normal and mesoionic (MIC), also called abnormal N-heterocyclic carbenes, *a*-NHCs (NHCs derived from imidazole and MIC or *a*-NHCs derived from 1,2,3-*1H*-triazole, respectively) have recently gained a prominent place in the organometallic chemist's toolbox due to their outstanding binding affinities to main group elements and transition metals, including copper(I). Indeed, the use of copper(I) complexes of NHC ligands as catalysts for CuAAC—following the pioneering work by Nolan and Diéz-Gonzaléz has turned out to be highly efficient.[6] Importantly, Cu(I)-NHCs are bench-stable complexes that are not easily oxidized in solution under reaction conditions, allowing reducing-agent free reaction procedures. Noteworthy, undesired Cu(I)-induced free radical side reactions as well as back addition of reduced ascorbic acid do not occur with Cu(I)-NHC catalyst, thus allowing reaction to proceed with sensitive substrates such as peptides.[6l] These discoveries have stimulated researches on the catalytic potential of Cu(I)-MIC systems in the context of the click chemistry and it turned out that these systems are excellent catalysts.[6o,p]

Some of us have reported that the scope of the Cu(I)-NHCs, especially with NHC = SIMes, can be extended by adding additional aromatic *N*-donor ligands such as 1,10-phenanthroline or 4,7-dichloro-1,10-phenanthroline.[6j,k] Using the latter additive, the solubility of the catalyst is improved in various solvents and the cycloaddition rate increases dramatically. Therefore, the CuAAC reactions could thus be performed under conditions other than neat or 'on water'. A lengthening of the chloride–copper bond—as evidenced both by DFT[6k] and X-ray crystallographic data[6m] —reflects the decrease of this bond strength and thus an easier hydrolysis affording the actual catalytic species. Naturally, we

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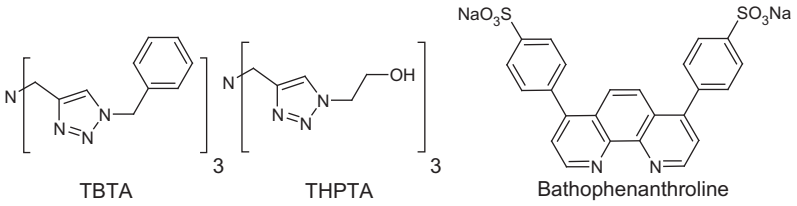
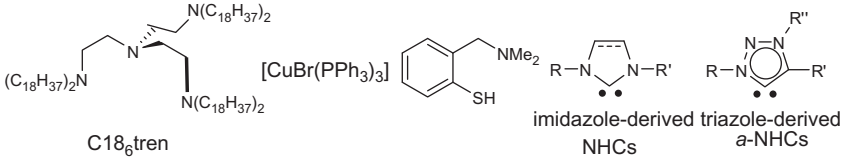
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.01.054



Scheme 1. Nitrogen ligands for Cu(II).



Scheme 2. Examples of N, P-, S-, and C-ligands for Cu(I).

were interested in testing the effect of combining Cu(I)-MICs and several nitrogen donors, expecting a marked enhancement of the catalytic efficiency.

We first tested the effect of such a combination with the Cu(I)-a-NHCs (**1**) and (**2**),[6m,7] combined with additives **3**–**6** to catalyze the reaction of phenylacetylene **7** with benzyl azide **8** to form 1-benzyl-4-phenyl-1,2,3-1*H*-triazole (**9**) in *tert*-butanol/water (2/1) at room temperature (Scheme 3, Table 1).

According to the click criteria, no precaution was taken to exclude oxygen. To discriminate between the catalysts, the reaction time was fixed at 4 h (except for the blank experiments, entries 1–2) and the product (**9**) was recovered by a simple filtration.

Regardless the reaction time (entries 1–4), a low conversion was observed with both Cu(I)-MICs **1** and **2** in solution. In the presence of 0.5 mol % of additive **3** the solution became immediately yellow-orange, this color being indicative of the formation of a soluble copper(I)–phenanthroline complex. This resulted in improved isolated yields of **9** with 30% and 60% being recovered after only 4 h reaction time (entries 5 and 6). After these experiments, the effect of substituents on the phenanthroline ligands was considered. Introduction of electron-donating methoxy groups (additive **4**) resulted in a deleterious effect (entries 7, 8). Indeed, the reaction mixture turned rapidly greenish indicating an oxidation at the copper center. On the contrary, additive **5**, possessing two electron-withdrawing chlorides allowed a rapid and high-yielding reaction (86% and 81%, entries 9 and 10). Entries 11 and 12 show that 1,1′-bipyridine **6** did not allow a good conversion. Overall, similarly to the NHC series, these results point out that **5** (4,7-dichloro-1,10-phenathroline) is the best additive for both Cu(I)-MICs. The catalytic system was tested on electron rich and poor alkynes as depicted in Table 2.

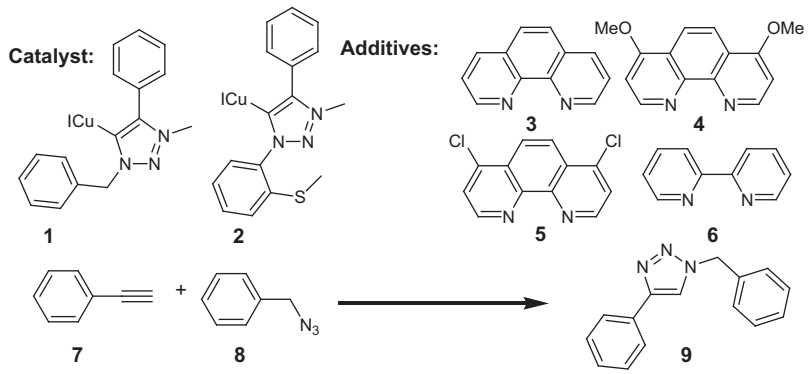
The reactions works equally well with rich (entry 2) or poor (entry 3) alkynes. In the case of 2-ethynyl anisole an exothermic reaction takes place with a completion (tlc) reached in few minutes.

To get more information about the compared efficiency of copper(I) systems containing normal and mesoionic NHCs, the formation of triazole **9** in wet methanol was followed by ^{1}H NMR with the systems **1+5** and **12+5** and compared with the stable complex

Table 1
Screening of the catalytic system[a]

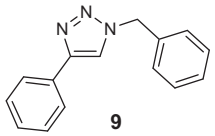
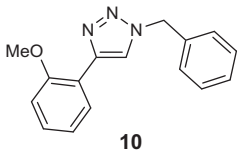
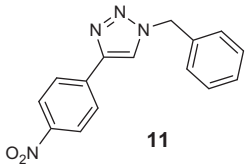
Entry	Catalyst[b]	Additive[c]	Time (h)	Isolated yield
1	**1**	None	24	20%
2	**2**	None	24	5%
3	**1**	None	4	Traces
4	**2**	None	4	Traces
5	**1**	**3**	4	62%
6	**2**	**3**	4	30%
7	**1**	**4**	4	17%
8	**2**	**4**	4	14%
9	**1**	**5**	4	86%
10	**2**	**5**	4	81%
11	**1**	**6**	4	33%
12	**2**	**6**	4	18%

[a] All reaction performed in *tert*-butanol/water (2/1) at room temperature.
[b] Catalyst loading: 0.5 mol %.
[c] Additive: 0.5 mol %.



Scheme 3. CuAAC reactions in solutions with NHC catalysts and N-donors as additives.

Table 2
Examples of synthesized triazoles[a]

Entry		Isolated yield (%)
1	 **9**	91
2	 **10**	86
3	 **11**	95

[a] All reactions performed in *tert*-butanol/water (2/1) at room temperature during 24 h; catalyst and additive loading: 0.5 mol %.

13 (conversion vs time are plotted in Fig. 1).[8,6k] The complex **12** corresponds to the iodo derivative of the Fukuzawa's catalyst [CuCl(TMes)].[6o]

All the kinetic curves exhibit an inductive period after which an acceleration of the catalysis is observed. The mesoionic systems

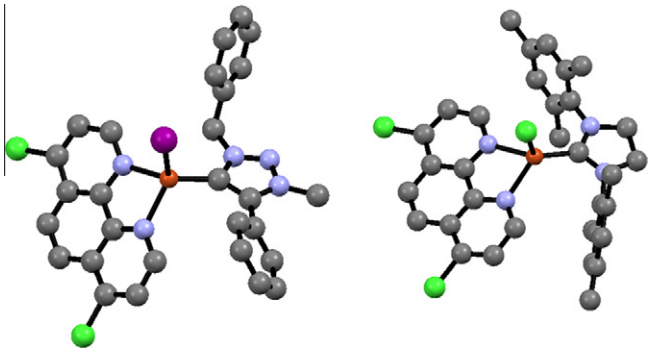
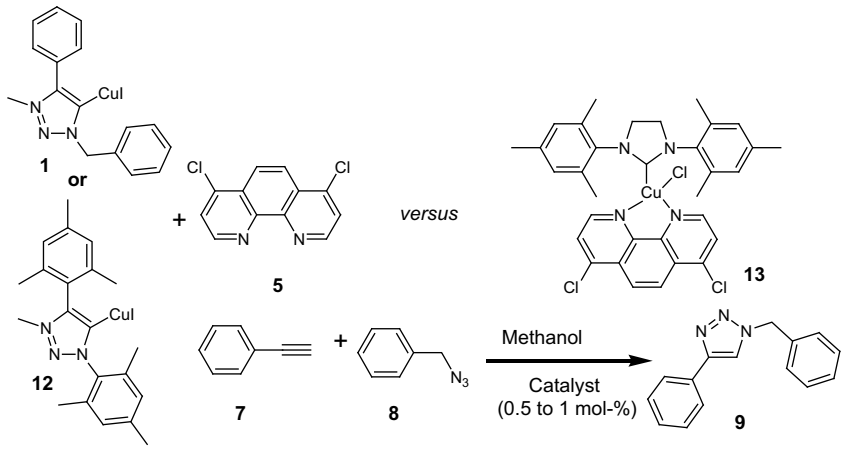


Figure 2. Views of complexes **1+5** (left, DFT) and **13** (right, X-ray)[6m] (gray: carbon, green chloride, blue: nitrogen, orange: copper and purple: iodide).

Table 3
Selected distances (Å) and $\%V_{bur}$

	1+5 (DFT)	**13** (X-ray)[6m]
C–N	2.05	2.12
C–Cu	1.92	1.90
$\%V_{bur}$ (d = 2.8 Å)	31.6	35.2
$\%V_{bur}$ (d = 3.5 Å)	30.7	37.2

1+5 and **12+5** displayed higher reaction rates than the 'classical' NHC **13**. This observation could result from the strong σ-donor character of MICs.[6q]



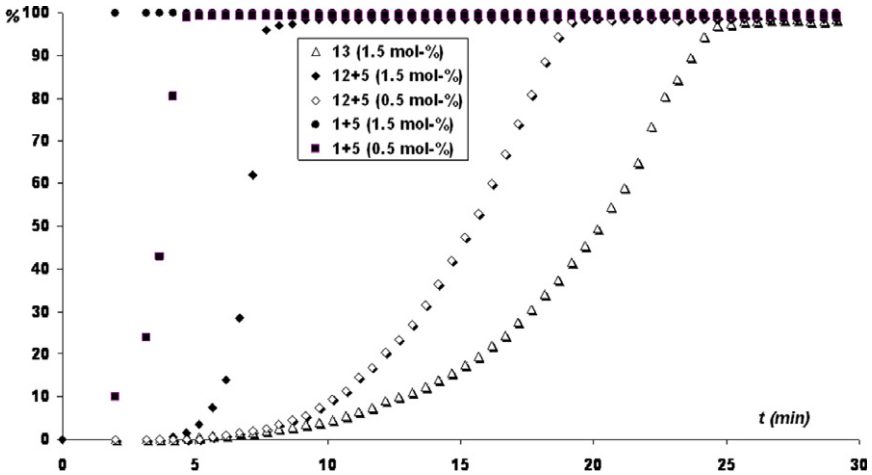
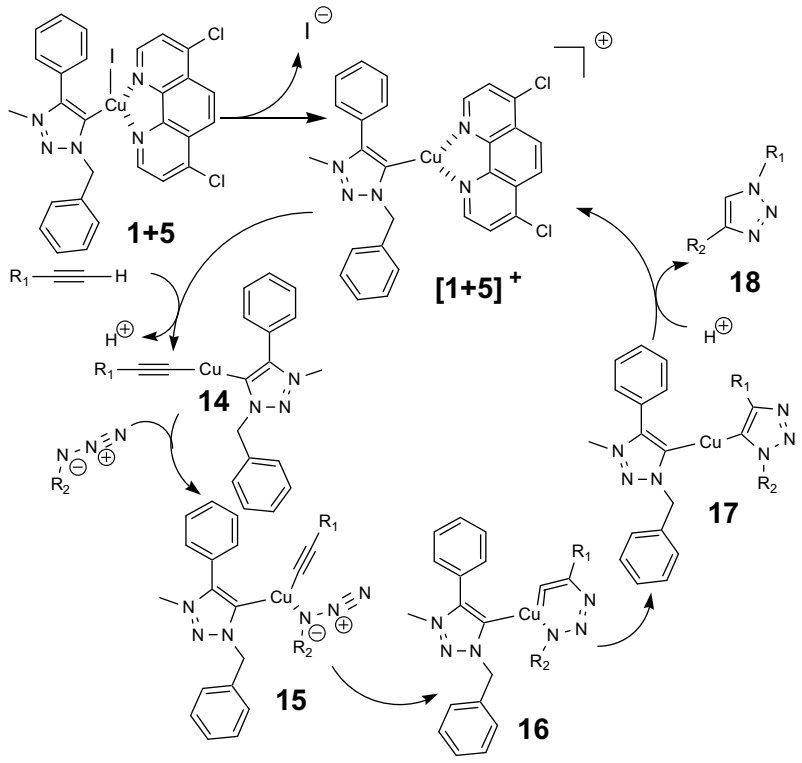


Figure 1. Kinetics of the formation of **9** at 298 K in methanol.



Scheme 4. Catalytic cycle leading to the formation of 1,2,3-triazole.

Among the mesoionic systems **1+5** (1.5 mol %) is highly active as a total conversion is reached before we were able to record the first scan during the NMR experiment (2 min). However, measurements become possible by lowering the amount of catalyst to 0.5 mol %. Under this condition, a total completion is observed after 5 min. The second mesoionic system (**12+5**) is also an excellent catalyst but its performance stays below.

In order to accede to the catalyst's structure we tried to grow X-ray suitable crystals from an equimolar mixture of **1** and **5**, but unfortunately, the crystallization attempts were not successful. Therefore, DFT calculations for the complex formed by the association of **1** with **5** were performed in the gas phase[9] and compared with the X-ray structure of **13** (Fig. 2).[6m]

In both cases, the copper(I) atom adopts a distorted tetrahedral geometry. The comparison of the Cu–N and Cu–C distances for the two complexes shows a fairly similitude (Table 3). A simple glance at the copper environment shows that the 'wings' of the NHC complex **13** are oriented toward the metal whereas for the mesoionic complex, the benzyl group does not efficiently shield the copper centre. This results in a visibly more crowded environment for the copper(I) in **13**. The $\%V_{bur}$ parameter has been introduced to measure the steric crowding—that is the accessibility of the metal center—associated to carbenic ligands.[10]

As depicted in Table 3, $\%V_{bur}$ values computed at 2.8 and 3.5 Å confirm that the catalytic center is significantly less hindered in the mesoionic carbene than in the NHC. Overall, the copper(I) atom is well protected in **13** but more accessible in **1+5**. Apart from stronger σ-donor character of MICs versus NHCs, the easier accessibility to the metal center could also explain the higher reaction rate observed for **1+5**.

Regarding mechanistic considerations, addition of the phenanthroline derivative **5** on the copper(I) complex **1** likely affords the cationic complex **[1+5]** in which the copper–iodide bond has been broken (indeed, the tri-coordinated $[(IPr)Cu(Phen)]^+$ has been crystallized and reported in the literature).[11] This step could be responsible for all the inductive periods observed in Figure 1. The resulting cationic copper(I) MIC–phenanthroline complex reacts with an alkyne to form the neutral copper–acetylide species **14**. Association with an azide yields **15** which forms transiently metallacycle **16**, then triazolide **17**,[12] which upon protonation affords the expected triazole **18** and regenerates the cationic catalyst [**1+5**] (Scheme 4).

In conclusion, we have reported that the association of 1,10-phenanthroline, especially the 4,7-dichloro derivative, with a copper(I) mesoionic N-heterocyclic carbene affords a catalytic system that surpasses the performances of a 'normal' NHC. This phenomenon could be explained by the combination of a greater electron-donating character of the carbenic ligand[6q] and a less crowded environment of the catalytic center.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.054.

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7. Compound **1**: (1-Benzyl-3-methyl-4-phenyl-1*H*-1,2,3-triazol-3-ium-5-ylidene)(iodido) copper(I). Compound **2**: (Iodido){3-methyl-1-[2-(methyl thio)phenyl]-4-phenyl-1*H*-1,2,3-triazol-3-ium-5-ylidene} copper(I).
8. ^{1}H NMR spectra were recorded with a Bruker Advance 500 spectrometer in MeOH using external D_2O with [alkyne] = [azide] = 0.5 mol L^{-1}. 1,4-Dimethoxybenzene (0.125 mol L^{-1}) was used as internal standard, see Supplementary data of Ref. 6h for details. For reproducibility propargyl alcohol should be distillated.
9. (a) The complex structure was fully optimized using GAUSSIAN 09 with DFT/B3LYP/6-31G(d,p) level for atoms as copper, carbon , Nitrogen, hydrogen and DFT/6-311G(d) level for iodide, this last basis set was extracted from basis set exchange database.; (b) For GAUSSIAN 09: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B., et al. *GAUSSIAN 09, Revision A.1*; Gaussian, Inc.: Wallingford CT, 2009.; For basis set exchange: (c) Glukhovstev, M. N.; Pross, A.; McGrath, M. P.; Radom, L. *J. Chem. Phys.* **1995**, *103*, 1878–1885; (d) Feller, D. *J. Comput. Chem.* **1996**, *17*, 1571–1586; (e) Schuchardt, K. L.; Didier, B. T.; Elsethagen, T.; Sun, L.; Gurumoorthi, V.; Chase, J.; Li, J.; Windus, T. L. *J. Chem. Inf. Model.* **2007**, *47*, 1045–1052. This methodology has proven to be successful for complex **10** as the calculated structure is in very good agreement with the X-ray one (see Refs. 6h,j, respectively).
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