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A Highly Active Catalyst for Huisgen 1,3-Dipolar Cycloadditions Based on the Tris(triazolyl)methanol−Cu(I) Structure

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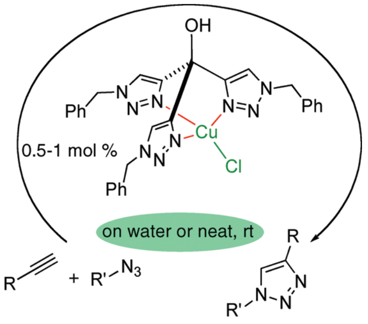
ABSTRACT



A new tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol ligand 3 has been prepared by a triple Cu(I)-catalyzed alkyne−azide 1,3-dipolar cycloaddition (CuAAC). Ligand 3 forms a stable complex with CuCl, which catalyzes the Huisgen 1,3-dipolar cycloaddition on water or under neat conditions. Low catalyst loadings, short reaction times at room temperature, and compatibility with free amino groups make 3·CuCl an outstanding catalyst for CuAAC.

Following its independent discovery by Meldal[1] and Sharpless,[2] the regioselective, Cu(I)-catalyzed alkyne−azide 1,3-dipolar cycloaddition (CuAAC) reaction has become the archetypal example of "click chemistry",[3] and the process has found application in almost every field of chemistry.[4]

In CuAAC reactions, a mixture of $CuSO_4$ and sodium ascorbate has been traditionally used as a precatalyst system which generates the Cu(I) species in the reaction media.[2] Later, it was discovered that polydentate nitrogen ligands not only stabilize Cu(I) intermediates[5] but also accelerate the catalytic process,[6] and this allowed the direct use of Cu(I) salts as catalysts in CuAAC reactions. Indeed, a tris(triazolylmethyl)amine **1** (Figure 1) was found to be an excellent ligand for this chemistry.[7] Tripodal tetraamino ligands like **2**[8] and *N*-heterocyclic carbenes[9] have also been successfully used to stabilize the catalyst in CuAAC.

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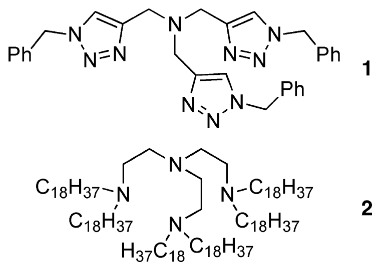

Figure 1. Polydentate N ligands for CuAAC.

Scorpionate ligands based on tris(pyrazolyl)borate moieties (Figure 2, top) form very stable metal complexes due to the establishment of chelated, cage structures involving the formation of six-membered rings.[10] These complexes have found ample application as catalysts in a variety of relevant processes and, most notably, in C−H bond activation methods.[11] We wondered whether the analogous tris(triazolyl)methane complexes would depict similar stability and, in particular, if the corresponding Cu(I) complexes would consequently perform as highly efficient catalysts in CuAAC. In fact, DFT theoretical calculations (B3LYP/LANL2DZ) performed on Cu(I) complexes of both types of structures revealed essentially identical structures for both types of complex (Figure 2, bottom). Thus, the Cu−N optimized distance has average values of 2.179 Å (c) and 2.188 Å (d), while the Cu−Cl-optimized distances are 2.317 Å (c) and 2.260 Å (d).

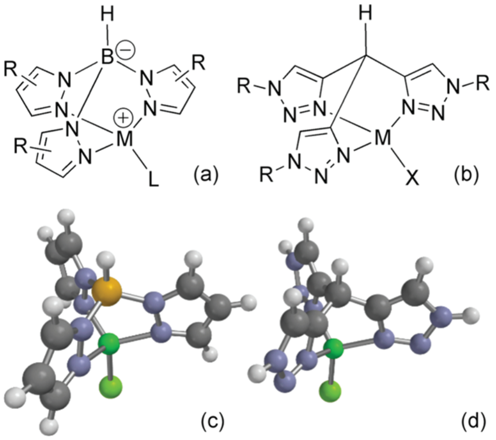

Figure 2. Top: Schematic representation of metal complexes of a tris(pyrazolyl)borate (a) and of a tris(triazolyl)methane (b). Bottom: DFT (B3LYP/LANL2DZ)-optimized geometries of the CuCl complexes of a tris(pyrazolyl)borate (c) and of tris(triazolyl)methane (d).

We accordingly envisioned that tris(triazolyl)methanol **3** (Figure 3), constructed in turn through a "click" approach, could be an outstanding ligand for CuAAC. In effect, besides the presumed stability of its Cu(I) complex, the molecule presents two well-differentiated faces with complementary hydrophobic and hydrophilic characters that make it ideal for work *on water*, a most usual condition for CuAAC.[12] In addition, due to its modular construction,[13] **3** could be readily fine-tuned for specific applications by simply changing the nature of the azido compound employed for its synthesis. On the other hand, the hydroxyl group placed on the hydrophilic hemisphere of the molecule can also serve as an anchor for supporting **3** onto polymeric materials.[14]

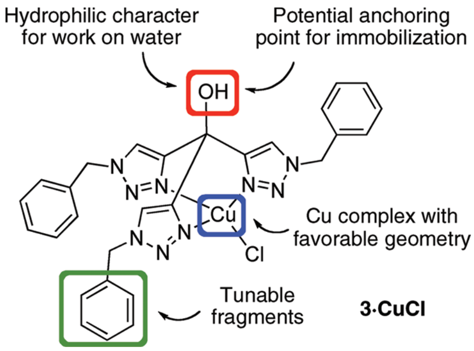

Figure 3. Structural features of **3·CuCl**.

The synthesis of **3** was planned through the intermediacy of tris(alkynyl)carbinol **4**[15] which, in turn, was readily prepared by addition of trimethylsilylacetylide to ethyl chloroformate (Scheme 1).

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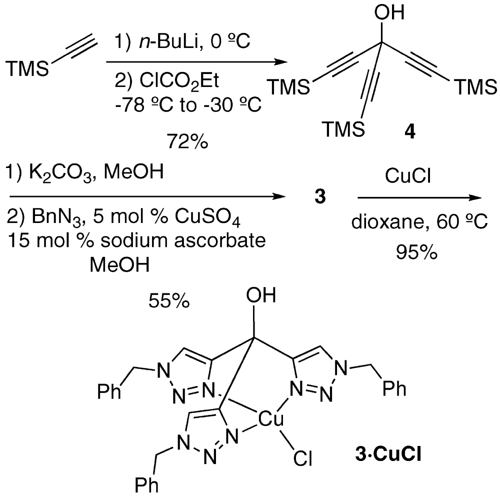
Scheme 1. Synthesis of the Tris(triazolyl)methanol/copper(I) Complex **3·CuCl**

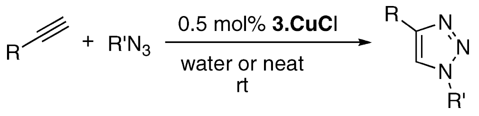


Subsequent deprotection of the TMS groups with K_2CO_3 in methanol followed by cycloaddition with benzyl azide under the classical CuAAC conditions ($CuSO_4$, sodium ascorbate) led to the target tris(triazolyl)methanol **3**[16] in good overall yield. The final copper catalyst **3·CuCl** was easily prepared by treatment of **3** with 1 equiv of CuCl in dioxane. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, and hexane was added to the solution. A greenish solid (**3·CuCl**) precipitated inmediately and was isolated in almost quantitative yield.

Most gratifyingly, **3·CuCl** turned out to be air and moisture stable. Although we have been unable to grow single crystals of **3·CuCl**, the coordination environment around copper can be inferred from the symmetry of the NMR spectra. In addition, a $CuCl_2$ complex of **3** presents in its crystal structure a hexacoordinated copper atom surrounded by two molecules of **3** acting as tridentate ligands (see the Supporting Information for details). The new catalyst was then tested in the CuAAC of benzyl azide and phenylacetylene under different experimental conditions. To our satisfaction, **3·CuCl** exhibited very high catalytic activity under mild reaction conditions, especially when water was present in excess in the reaction media. In fact, reactions were fast at room temperature under neat conditions or in the sole presence of water, with catalyst loadings of only 0.5 mol %.

The scope of applicability of **3·CuCl** was explored under these conditions (Table 1). Catalyst loadings as low as 0.25 mol % could be used too, but at the expense of longer reaction times. This decrease in reactivity was compensated by carrying out these reactions at 40 °C (Table 1, entries 9−11). As the inspection of Table 1 reveals, excellent yields are generally obtained in the CuAAC of a wide variety of alkyne with alkyl, benzyl, or aryl azides.

Table 1. CuAAC Using Catalyst **3·CuCl**



entry	R	R′	prod	time (h)	yield^{a} (%)
1	Ph	Ph	**5a**	4	99^{b}
2	Ph	*n*-Oct	**5b**	4	99^{b}
3	Ph	$PhCH_2$	**5c**	4	94^{b}
4	Ph	$PhCH_2$	**5c**	15	99^{c}
5	CO_2Et	*n*-Oct	**5d**	15	99^{b}
6	CH_2NMe_2	Ph	**5e**	4	95^{b}
7	2-pyridyl	$PhCH_2$	**5f**	8	99^{b}
8	$PhCH_2CH_2$	$PhCH_2$	**5g**	4	99^{c}
9	*n*-Bu	$PhCH_2$	**5h**	16	98^{b,d}
10	*n*-Hex	$PhCH_2$	**5i**	16	98^{b,d}
11	4-chlorobutyl	$PhCH_2$	**5j**	18	64^{b,d}
12	CO_2Et	$PhCH_2$	**5k**	12	96^{b}
13	*p*-$HOCH_2C_6H_4$	$PhCH_2$	**5l**	2	92^{b}
14	CH_2OH	$PhCH_2$	**5m**	6	84^{b}
15	CH_2NMe_2	$PhCH_2$	**5n**	4	97^{b}
16	CH_2NH_2	$PhCH_2$	**5o**	5	47^{e}

^{a} Isolated yield. ^{b} Water. ^{c} Neat. ^{d} 0.25 mol % of catalyst at 40 °C. ^{e} 1 mol % catalyst in *n*-BuOH/water 2:1 and basic workup.

The result obtained in the cycloaddition of propargylamine with benzyl azide (entry 16) deserves special comment. In general, the CuAAC fails in the presence of free amino groups due to the strong tendency of amines to form complexes with Cu(I), thus deactivating the catalyst. With the use of **3·CuCl**, this deactivation did not occur, and the corresponding triazole product could be isolated in 47% yield. This result shows how the tight complexation present in **3·CuCl** can allow avoiding additional protection and deprotection steps when free amines have to be involved in CuAAC.

Taking into account the interest of avoiding storage and manipulation of organyl azides, the use of **3·CuCl** in a one-pot process involving the in situ formation of a benzyl-type or alkyl (octyl) azide from the corresponding bromides and sodium azide was explored (Table 2).

This tandem process performed nicely in water using a 1 mol % catalyst at 40 °C (entries 1−7). A microwave-promoted version, which allowed substantial reduction of reaction times, was also set up. In this case, a 1:1 mixture of acetonitrile/water was used, as well as reaction temperatures of 100 °C. Under these conditions, reaction times as short as 40 min were sufficient to allow the isolation of the cycloaddition products in good yields (entries 8−13).[4g] It must be noted that, due to the lower reactivity of octyl bromide in front of sodium azide, 2 equiv of this reagent with respect to the alkyne was used.

Finally, **3·CuCl** was also used to catalyze the cycloaddition of **4** with benzyl azide in water leading to the tris(triazolyl)-methanol ligand **3**. In this way, the target tris(triazole) can be routinely prepared in gram amounts in 86% isolated yield (Scheme 2). With this improvement, **3·CuCl** can be prepared in only three steps from commercially available precursors in 59% overall yield.

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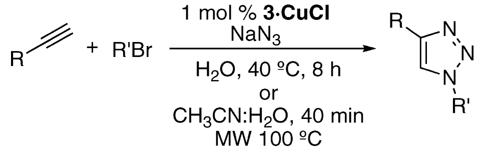
(16) Patent pending.

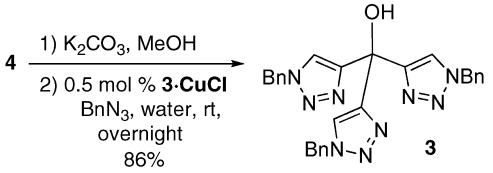
Table 2. One-Pot Azide Formation plus CuAAC Reaction Mediated by **3·CuCl**



entry	R	R′	prod	yield[a] (%)
1	Ph	$PhCH_2$	**5c**	99[b]
2	Ph	p-$^tBuC_6H_4CH_2$	**5p**	98[b]
3	Ph	p-$NO_2C_6H_4CH_2$	**5q**	98[b]
4	Ph	p-$MeOC_6H_4CH_2$	**5r**	93[b]
5	Ph	o-$ClC_6H_4CH_2$	**5s**	80[b]
6	Ph	m-$NO_2C_6H_4CH_2$	**5t**	88[b]
7	p-$HOCH_2C_6H_4$	p-$NO_2C_6H_4CH_2$	**5u**	90[b]
8	Ph	*n*-Oct	**5b**	57[c]
9	CH_2OH	*n*-Oct	**5v**	38[c]
10	CH_2OH	$PhCH_2$	**5m**	88[c]
11	CMe_2OSiMe_3	$PhCH_2$	**5w**	98[c]
12	CH(OH)Ph	*n*-Oct	**5x**	89[c]
13	CH_2SPh	*n*-Oct	**5y**	70[c]

[a] Isolated yield. [b] In water at 40 °C. [c] In acetonitrile/water at 100 °C, under MW irradiation.

Scheme 2. Improved Preparation of **3** Using Catalyst **3·CuCl**



In summary, ligand **3** turns out to be a simple yet powerful complexing agent for Cu(I). Indirect evidence (XRD and NMR) suggests that **3** forms a 1:1 complex with CuCl, with all three triazole moieties interacting with the metal center. Probably due to the tight protecting cage formed around the metal center and to its particular functional groups arrangement, catalyst **3·CuCl** behaves as a very active promoter of the CuAAC, as it has been demonstrated with a broad variety of substrates (including free amines) under different reaction conditions. Application of metal complexes of analogs of **3**, readily available by cycloaddition from the key intermediate **4**, to a variety of catalytic processes is currently underway in our laboratories.

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Supporting Information Available: Experimental procedures. Spectral and analytical data for all new compounds. Calculated atomic coordinates. Crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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