

**THE USE OF LIGANDS IN COPPER-CATALYZED [3+2] AZIDE-ALKYNE  
CYCLOADDITION: CLICKER THAN CLICK CHEMISTRY?**

Silvia Díez-González\*

*Department of Chemistry, Imperial College London  
Exhibition Road, South Kensington, SW7 2AZ London (UK)*

*[s.diez-gonzalez@imperial.ac.uk](mailto:s.diez-gonzalez@imperial.ac.uk)*

*Phone: 0044(0)20759 49699*

*Fax: 0044(0)20759 45804*

## Abstract

The last decade has witnessed a tremendous increase of the studies concerning [3+2] cycloaddition reactions of azides and alkynes. The recent discovery of copper(I) species as efficient catalysts for this transformation is at the origin of this true explosion. In contrast with classical thermal reactions, copper catalysis leads to the *regioselective* formation of 1,4-disubstituted 1,2,3-triazoles in high yields and under simple reaction conditions. This transformation has indeed become the most prominent example of the principles of Click chemistry, postulated in 2001 by Sharpless and co-workers.

Despite the ever-increasing interest in this process, the use of ligands in this context remains minor when compared to ligandless systems. Nevertheless, besides overcoming the inherent limitations of ligandless systems, the use of ligands in this context has been shown to increase and, more importantly, modulate the catalytic activity of the metal center. Herein, the catalytic activities of ligated copper systems are reviewed in a way intended inspirational for future developments in this field.

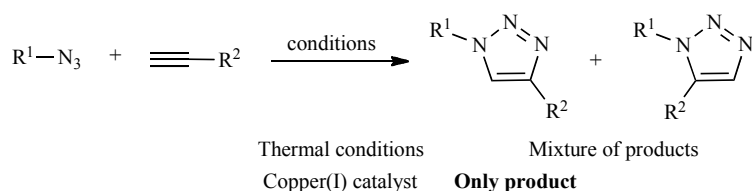
## Keywords

Alkyne – Azide – Click – Copper – Cycloaddition – Ligand

## 1. Introduction

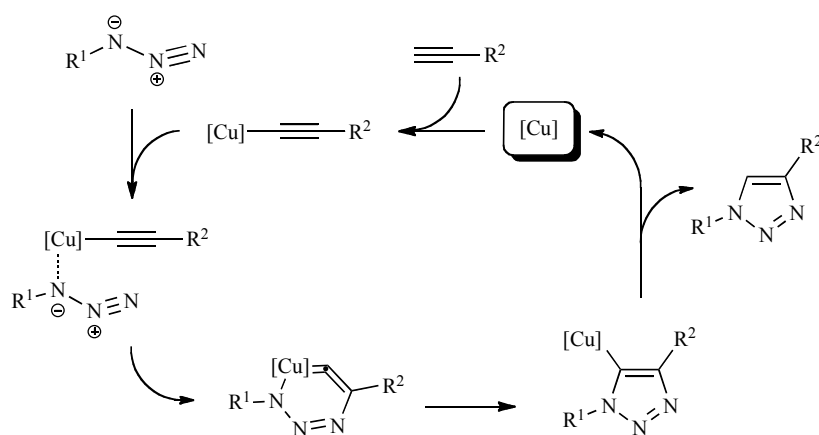
Modern molecular chemistry is in continuous quest for more efficient and less contaminating processes capable of providing an ever-increasing number of complex molecules and/or architectures. The notion of Green Chemistry arose from this problematic and is widely applied in academia even if it was originally intended for industrial applications.<sup>1</sup> Only three years after Anastas postulated the 12 principles of Green Chemistry,<sup>2</sup> Sharpless and co-workers introduced the concept of Click Chemistry, and the criteria for a transformation to be considered as Click.<sup>3</sup> Inspired by Nature, the objective is to rapidly create molecular diversity through the use of reactive modular building blocks and only benign reaction conditions, simple work-up and purification procedures. Most common carbon–heteroatom bond forming reactions could be considered Click if they fulfilled the following basic requirements: no sensitivity towards moisture or oxygen, high yields and stereospecificity, absence of solvent (or use of a benign one) and simple product isolation.

Even if L'abbé first observed the good activity of copper(I) in [3+2] cycloaddition reactions in 1984,<sup>4</sup> it was not until 2002, when Sharpless<sup>5</sup> and Meldal<sup>6</sup> revolutionized this research field with their independent reports on the efficiency of copper(I) species as catalysts for a particular 1,3-dipolar Huisgen cycloaddition:<sup>7</sup> the reaction of organic azides and terminal alkynes to yield 1,2,3-triazoles (Scheme 1). Outstandingly, under such conditions, the reactions were completely regioselective and only 1,4-disubstituted triazoles were formed, in contrast with the mixture of regioisomers obtained under classical thermal conditions. Since, this copper-catalyzed azide-alkyne cycloaddition (CuAAC) has become the most popular Click reaction developed to date.



**Scheme 1.** 1,2,3-Triazoles synthesis.

Early mechanistic studies led to the proposal of the stepwise catalytic cycle depicted in Scheme 2.<sup>8</sup> In a first stage, the starting alkyne would react with the copper(I) species to form an acetylide-copper complex that would interact with the azide activating it toward nucleophilic attack of the acetylide carbon to the ‘external’ nitrogen atom of the azide and generating a metallacycle. Subsequent ring contraction would generate a copper-triazolide, direct precursor of the reaction product upon protonation.



**Scheme 2.** Proposed mechanism for the CuAAC.

Further studies showed that in most cases, the reaction is second order in copper, probably due to the dynamic equilibrium of different **copper**-acetylides existing in solution. In fact, there is increasing evidence favoring bi- or polynuclear pathways for this reaction.<sup>9, 10</sup>

Independence of the uncertainty around the mechanism, this reaction has attracted an enormous interest and its applications are still increasing exponentially. Due to the known instability of numerous copper(I) species, the active species are generally generated *in situ* from a copper(II) salt and a reducing agent (most often sodium ascorbate). These systems can be extremely efficient, but they are intrinsically limited to water-tolerant substrates and only marginal leeway is left for unsuccessful reactions. Alternatively, the addition of ligands can not only protect Cu<sup>I</sup> centers, but also greatly improve their activity, allowing for smoother reaction conditions or broader applicability. The families of ligands studied so far are very diverse and possess very distinct stereoelectronic properties, which make it even more difficult to understand the whole mechanistic picture for this transformation. **Furthermore, the reports comparing different families of ligands remain scarce.**<sup>11, 12</sup>

This review intends to provide an overview of the activity of ligated copper species in the cycloaddition of azides and alkynes. Even if application examples of the discussed catalytic systems will be mentioned, it is out of the scope of this review to comment them all and for this purpose, the reader should refer to

one of the abundant reviews available.<sup>13-23</sup> Instead, this review will focus on the particularities of each catalytic system and their adjustment to the Click criteria.

## 2. Nitrogen-Based Ligands

Nitrogen containing ligands have been the first and the most widely employed ligands for CuAAC. In numerous applications the N-containing additive is merely referred to as a base, even though their affinity for copper is well-known. Alternatively, such additives are usually referred to as a straightforward way of increasing the solubility of copper(I) species in the reaction media, particularly when commercially available complexes such as  $[\text{Cu}(\text{NCMe})_4]\text{PF}_6$  are employed with no other binding agent in the reaction mixture.<sup>24, 25</sup> Additionally, chelating azides have been shown to facilitate the copper(II) acetate accelerated CuAAC.<sup>26</sup> Despite the plethora of applications these ligands have found to date, the nature of the actual active catalyst has scarcely been studied, leaving plenty of room for further investigation/improvements. Also, comparative studies with different nitrogen-based ligands are extremely rare.<sup>27</sup>

### 2.1. Amine Ligands

A number of very simple tertiary amines have been used as base/ligands in the CuAAC reactions. They are often combined with other stronger ligands, although they have also been used in the absence of any other additive. Triethylamine is one of the most common ones, and such a simple additive is capable of stabilizing the copper(I) centers in a number of applications,<sup>28-30</sup> even for reactions carried out 'on water'.<sup>31-33</sup> Other readily available amines have been employed (Figure 1),<sup>34, 35</sup> but regrettably, no studies have been conducted to determine the nature of the coordinated species responsible for the catalytic activity, or the influence of the substituents on the nitrogen atom. Unarguably, the most popular amine of this series is the Hünig's base, diisopropylethylamine (DIPEA). Not only it can be considered as the first ligand applied to this transformation –it was used in the groundbreaking work by Meldal *et al.*–<sup>6</sup> but also it has become a well-established Click protocol not only in immobilization processes as in the original report, but also in the preparation of peptides<sup>36</sup> and other biomolecules<sup>37, 38</sup> as well as macrocycles,<sup>39, 40</sup> to name some examples.

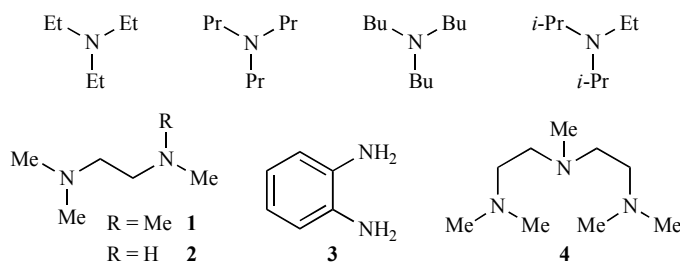
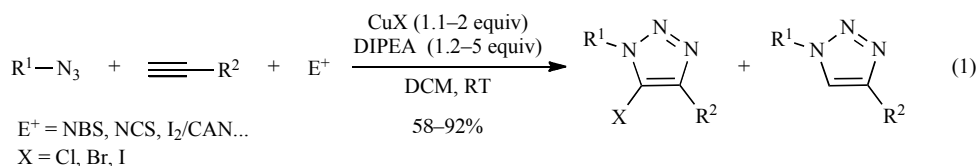


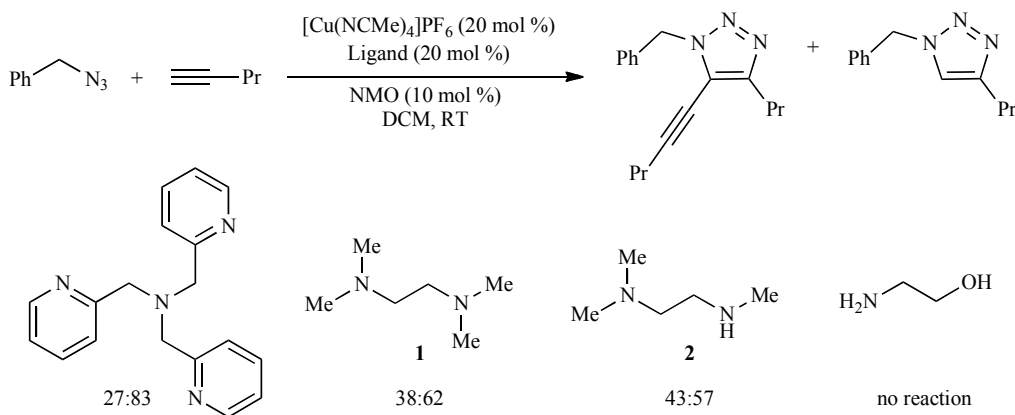
Figure 1. Amines used in CuAAC

Additionally, DIPEA was also employed in a tandem CuAAC/electrophilic addition to prepare a number of 4,5-functionalized triazolyl-nucleosides (Eq 1).<sup>41</sup> In this process, the presence of all protic sources had to be avoided to overcome the proteolysis of the copper-triazolide intermediate leading to 'regular' 5-H-triazole products. Hence, the amine served not only as ligand and base in the copper-acetylide formation,

but also as proton sponge for any acid coming from the electrophilic agent. Despite the precautions, different mixtures of products were obtained in all cases (30–95% selectivity) and column chromatography was required to purify the resulting triazoles. Furthermore, stoichiometric amounts of copper salts were compulsory to ensure moderate to good reaction yields.



Under certain conditions, the copper-triazolyde species can be trapped with the starting alkyne instead. For this, a diamine ligand was required to maximize the products ratio (1,4,5-trisubstituted *vs* 1,4-disubstituted triazoles).<sup>42</sup> Even if the nature of the copper active species in the coupling process could not be determined, the presence of an oxidant in the reaction mixture points towards the involvement of copper(II)/copper(III) species. Furthermore, very interesting reactivity trends were observed when different bidentate ligands were screened for this transformation (Scheme 3). In particular, whereas peralkylated ligands (**1**) privileged the formation of disubstituted triazoles, ligands with N–H bonds (**2**) favored trisubstituted products. Of note, the addition of 1 equiv of DIPEA further increased the formation ratio of such products (up to 75:25). Moreover, no reaction at all was observed when using hydroxyl amine ligands. This is surprising since even if oxygen-based ligands have not been studied *per se* for the CuAAC, N,O mixed ligands have been found suitable in this context (*vide infra*). Overall, up to 68% of trisubstituted triazoles could be isolated after column chromatography, along with the corresponding 1,4-disubstituted analogues.

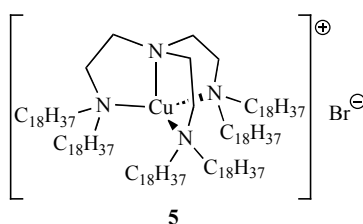


**Scheme 3.** Ligand influence in the preparation of 1,4,5-trisubstituted triazoles.

Diamine ligands have also been employed in other applications of CuAAC, such as **2**, used in the functionalization of polypeptides,<sup>43</sup> or phenylenediamine **3**, which showed a remarkable activity for the cycloaddition of different alkynes and glucosyl azides in water.<sup>44</sup>

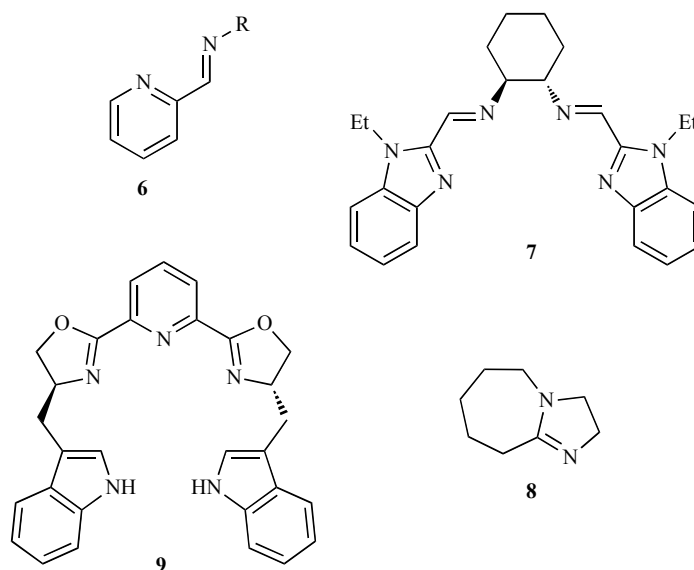
On the other hand, a triamine ligand, pentamethylethylenetriamine **4** (PMDETA) is possibly the most commonly employed ligand in CuAAC. This is probably due to the well-established efficiency of CuBr/PMDETA in polymerization processes such as ATRP. A solid supported version on this catalytic system, based on poly(ethyleneimine), was recently reported.<sup>45</sup> However, it displayed a gradual decrease in activity when reused either because of oxidation of the copper(I) centers or metal leaching. Better

results were obtained with a copper(I)-tren complex **5**,<sup>46</sup> originally applied to ATRP processes. This crowded tripodal ligand effectively protected the copper center against oxidation while keeping it highly active for the cycloaddition reaction. This catalyst respected all Click requirements and in particular, solubility of **5** in the hydrocarbon solvents allowed for its separation from the reaction products by simple filtration. The separated filtrate could be reloaded with the starting azide and alkyne for a second reaction, whereas the separated triazoles showed only negligible copper contamination. The extremely high reactivity of this complex was illustrated by its application to the cycloaddition of an internal alkyne (see Section 4 for further details) and the preparation triazoles-linked dendrimers. Stoichiometric amounts of catalyst are generally required for the later application, since copper remains trapped inside the formed dendrimer. Nevertheless, only 0.1 mol % of **5** was enough to produce a dendrimer in good yield from a nona-azide. An all-methyl tren ligand has also been employed in the preparation of different macromolecules.<sup>47, 48</sup>



## 2.2. $N(sp^2)$ -Type Ligands

The first simple imine ligands applied to the Huisgen cycloaddition were pyridylimines **6** (Figure 2).<sup>49, 50</sup> These ligands showed a remarkable activity when used in one pot CuAAC/living radical polymerizations, both reactions proceeding simultaneously rather than sequentially.<sup>51</sup> One important drawback of these additives is their inherent instability (they need to be kept at 0°C under inert atmosphere) which preclude their use under Click-suitable conditions, at least when the coordinated copper species are generated *in situ*. Alternatively, stable tetradentate ligand **7** was reported to form a well-defined one-dimensional coordination polymer when reacted with CuI.<sup>52</sup> Either such polymer or a combination **7**/CuI were successfully applied to the cycloaddition of alkynes and *in situ* generated azides from the corresponding bromides. In these reactions, 2 mol % [Cu] were used at room temperature in a mixture MeCN/H<sub>2</sub>O. Even if no extrusion of oxygen or moisture was required, some of the formed triazoles had to be purified by column chromatography.



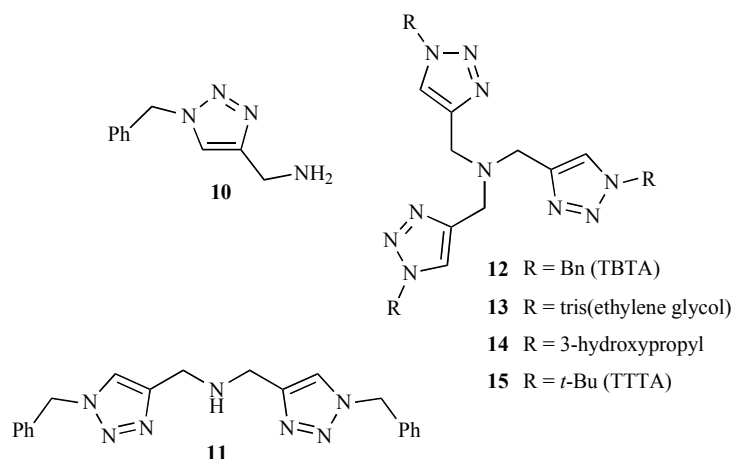
**Figure 2.** Imine ligands used in CuAAC reactions.

Other cyclic imines studied in this context include the commercially available 1,8-diazabicycloundec-7-ene **8** (DBU). Despite its availability, no methodological studies have been carried out with this ligand, maybe due to its high toxicity, incompatible with proper Click reactions. Nevertheless, DBU has been successfully used as only additive in the preparation of peptide analogues<sup>53</sup> and block polymers,<sup>54, 55</sup> as well as nanotube wall<sup>56</sup> and polymer functionalization.<sup>57, 58</sup> A related triazabicyclodecene scaffold has also been reported for the polymer-supported CuAAC.<sup>59</sup> Finally, pybox derivative **9** was applied to the kinetic resolution of prochiral azides through their cycloaddition with a terminal alkyne.<sup>60</sup> This work represents the first asymmetric induction reported for CuAAC, although only poor enantioselectivities were achieved.

Undoubtedly, the most commonly used cyclic imine-type ligands used in the cycloaddition of azides and alkynes are polytriazoles. As early as in 2003, and alerted by the observation of accelerating reaction rates in their preparation, the biocompatibility of this transformation using polytriazoles as ligands was demonstrated by the protein modification of *virus capsids*,<sup>61</sup> enzymes in living mice<sup>62</sup> and cell surface of *Escherichia coli*.<sup>63</sup> Since, the exponentially increasing applications of these ligands have been particularly focused, with notable exceptions,<sup>64-67</sup> on biological systems and protein labeling in particular. Consequently, the search for novel and improved fluorescent probes for this purpose is also an active field of research and has benefited from the good ligand properties of polytriazoles.<sup>68-70</sup> Even if sodium ascorbate can still be used as reducing agent in these sensitive applications,<sup>71-74</sup> tris(carboxyethyl)phosphine is a much popular reductant in this context thanks to its softness and ability to protect certain aminoacids residues in proteins from oxidative coupling.

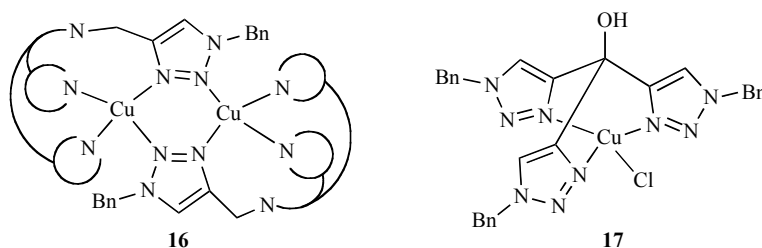
One year after the first application of polytriazoles as additives in CuAAC, a comparative study of different architectures was reported.<sup>75</sup> Different mono, bis and tris-triazoles were screened along with simple amines, diamines and pyridine derivatives. Remarkably, very different trends in reactivity were observed depending on the nature of the copper source; whereas amino-triazole **10** was the most competent ligand for CuSO<sub>4</sub>/NaAsc system, bistriazole **11** was the best performing when [Cu(NCMe)<sub>4</sub>]PF<sub>6</sub> was used instead (Figure 3). Tris(benzyltriazolylmethyl)amine (TBTA) **12** was also a

good ligand for the model reaction, although in a lesser extent (84% yield vs 94% with **11**). Still, tris(triazoles), and TBTA in particular, have virtually become the only triazoles used as ligands in CuAAC. A polymer-supported version of TBTA/CuI has also been reported.<sup>76</sup> Despite its easy recycling when 1 mol % [Cu] was used (ten successive runs without a significant yield drop), up to two days were required to form the expected triazoles in very high yields. Water-soluble triazoles such as **13**<sup>77</sup> and **14**<sup>78</sup> were also studied for different applications, and **14** in particular was shown to actively protect histidine residues in proteins against reactive oxygenated species in the reaction media.<sup>79</sup> In this example, since **14** is actually consumed as it gets oxidized, an excess of ligand had to be employed.



**Figure 3.** Triazole ligands in CuAAC.

The preparation of **16**, a well-defined copper(I) complex with TBTA **12**, notably established that (at least in the solid state) no metal coordination with the tertiary amine moiety occurs.<sup>80</sup> This air-sensitive compound displayed an unusual dinuclear structure with two copper centers in a distorted tetrahedral geometry bridged by two triazole units through their medial and proximal nitrogen atoms (Figure 4). Better catalytic results were obtained with related tris(triazolyl)methane complex **17**.<sup>81</sup> Based on the characterization data and the crystal structure of a copper(II) analogue, the structure shown in Figure 4 was proposed, although no crystals could be grown for this compound.

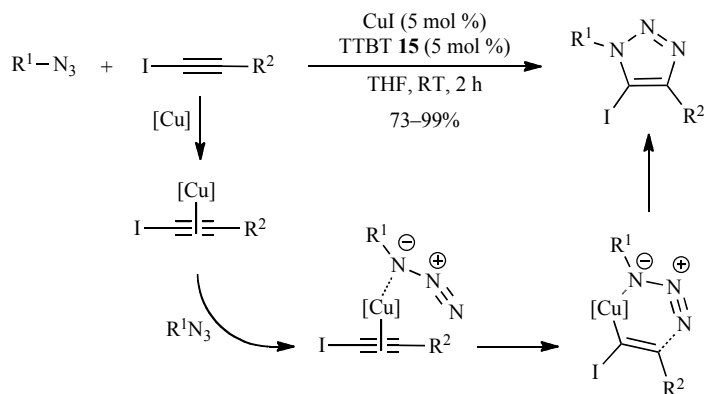


**Figure 4.** Well-defined triazoles-copper complexes in CuAAC.

Air stable complex **17** exhibited a remarkable activity in CuAAC and a variety of triazoles were prepared from the corresponding azides, either pre-isolated (0.5 mol % [Cu], water or neat, RT) or *in situ* generated (1 mol % [Cu], water, 40°C). As a drawback, the presence of free amines in the starting materials drastically reduced the reaction conversion.



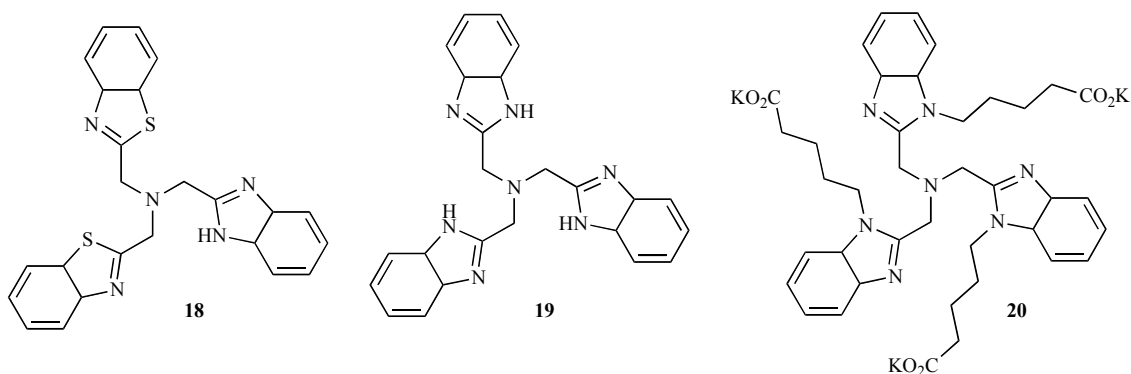
Additionally, polytriazoles ligands were proven crucial for the preparation of 1,4-disubstituted-5-iodotriazoles *via* the cycloaddition of organic azides and 1-iodoalkynes.<sup>82</sup> For these reactions TTAT **15** (Figure 3) was found superior to TBTA **12** and good to excellent yields were obtained at room temperature after short reaction times (Scheme 4). Of note, triethylamine was also found a good additive for this transformation, although 2 equivalents instead of 0.05 were required in that case.



**Scheme 4.** Cycloaddition of azides and 1-iodoalkynes.

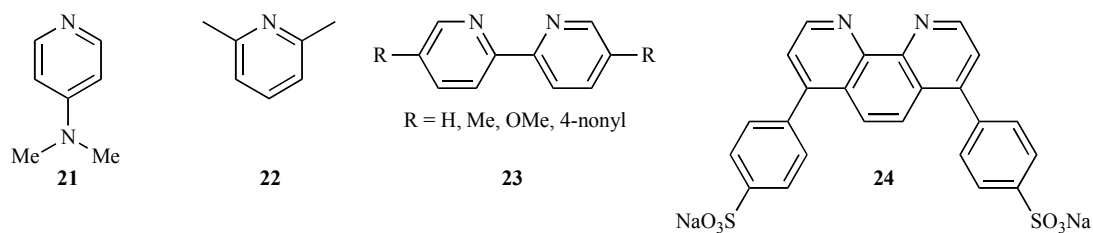
For this system,  $\pi$ -activation of the alkyne, rather than formation of a copper acetylide complex was proposed. The clean formation of the iodotriazoles was used to support this hypothesis since with a more traditional mechanism (Scheme 2), the copper-triazolide intermediate would be easily hydrolyzed into 5H-triazole as by-product. However, for this particular reaction, a sequence oxidant addition/cycloaddition/reductive elimination seems also plausible.

Diverse structures related to TBTA **12** have been prepared and screened in CuAAC (Figure 5).<sup>83, 84</sup> These studies particularly showed that the most performing ligands were different depending on the reaction conditions. Hence, whereas **18** displayed a good activity in a range of pH values under diluted biocompatible concentration, **19** and **20** were optimal for concentrated conditions. Furthermore, despite their similar structure, the best ratio metal/ligand changed from 1:1 for **19** to 2:1 for **20**. All these observations, along with the different kinetic data obtained according to the reaction conditions, reflect a very complicated mechanistic picture for these systems. It seems reasonable that the relatively weak chelating properties of these ligands, combined with the diverse copper coordination chemistry make such studies even more complicated and that the rate-limiting step may change easily depending on the reaction conditions.

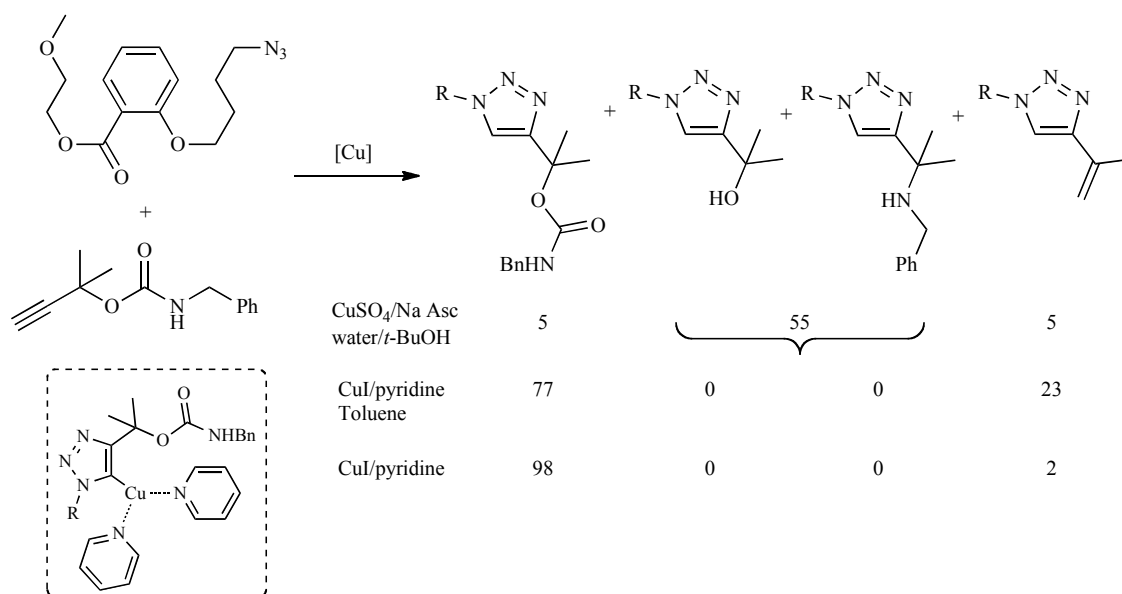


**Figure 5.** Benzimidazole/benzothiazole ligands for CuAAC.

Pyridine derivatives were also applied to CuAAC (Figure 6). Simple pyridine has notably been used in the absence of other additives for the preparation of peptidotriazoles<sup>85</sup> and linear polymers.<sup>86</sup> It is worth mentioning that for the particular case of propargyl carbamates, a mixture of triazoles products was unexpectedly obtained when the cycloaddition reaction was attempted with the CuSO<sub>4</sub>/NaAsc system (Scheme 5). On the contrary, excellent conversion into the expected triazole was observed when CuI/pyridine was used instead.<sup>87</sup> The authors rationalized that in this case, the postulated triazolide intermediate would be further coordinated with pyridine molecules, preventing the interaction of the copper center with the carbonyl group from the carbamate. Such interaction is expected to weaken the single C–O bond of the molecule, thus facilitating the cleavage of the carbamate function and leading to the formation of by-products.

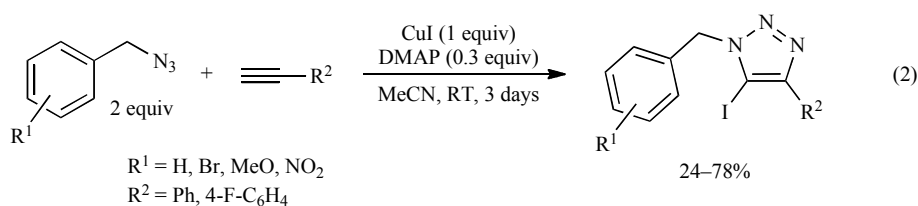


**Figure 6.** Pyridine derivatives for CuAAC.

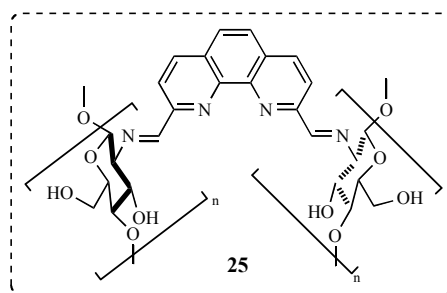
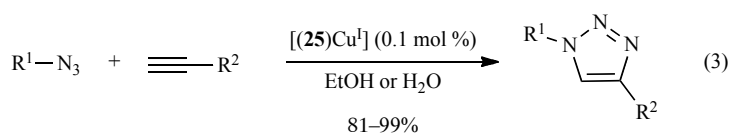


**Scheme 5.** Selectivity for CuAAC with propargyl carbamates.

Alternatively, it was observed that when DMAP (4-(dimethylamino)pyridine) **21** was used as additive in CuAAC, 5-iodotriazoles could be formed as major products instead of the expected 5-H-triazoles.<sup>88</sup> Of note, only the ‘regular’ triazoles were obtained when DIPEA or dimethylacetamide were used instead. The outcome of these reactions, stoichiometric in CuI, was strongly dependent of the relative concentrations of the different compounds in the reaction media. Under optimized conditions, a number of activated alkynes could be reacted with organic azides to yield 1,4,5-trisubstituted triazoles in low to fair yields after long reaction times (up to 3 days) (Eq 2).



Lutidine **22** is a popular pyridine-derivative in CuAAC. It has notably been used as the only additive in the cyclization of peptides,<sup>89</sup> functionalization of DNA<sup>90</sup> or human growth hormone,<sup>91, 92</sup> and the stabilization of organogels.<sup>47</sup> Alternatively, bipyridine and phenanthroline derivatives also showed remarkable ability to accelerate CuAAC. These electron-rich ligands were pointed out as remarkable ligands for this transformation quite early thanks to a fluorescence quenching assay,<sup>93</sup> and have been used in several applications, particularly in macromolecular science. For instance, bipyridines **23** have been used in the functionalization of polymers,<sup>94-96</sup> nanoparticles,<sup>97</sup> and nanocages<sup>98</sup> as well as the synthesis of cyclic polymers.<sup>99, 100</sup> The nature of the active species in these applications remains particularly elusive, since the copper/ligand ratios employed vary from Cu:L = 1:3 to 2:1. Sulfonated bathophenanthroline **24** was mainly been applied to the functionalization of biomolecules, instead, where it proved superior to standard TBTA **12** in some applications,<sup>101</sup> and remains one of the most accelerating ligands known for bioconjugation. Ligand **24** was applied, for example, to the derivatization of bionanoparticles,<sup>102</sup> and proteins.<sup>103-105</sup> Alternatively, a phenanthroline derivative was found optimal for the activity in CuAAC of a biopolymer supported catalysts (Eq 3).<sup>106</sup> Surprisingly, the supported copper(I) complex was more active than its homogeneous analogue. Reactions were carried out in ethanol or water with only 0.1 mol % [Cu] at 70°C to obtain the expected triazoles in high yields after simple filtration or recrystallization.

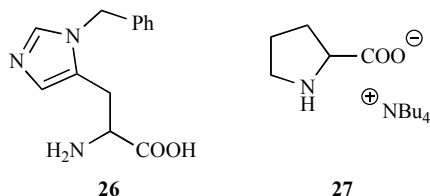


### 2.3 Mixed N,O Ligands

To the best of my knowledge, no reports on the activity of O-ligands have been reported so far for the CuAAC. However, there are some examples with N,O mixed ligands despite the lack of activity reported for hydroxylamines (Scheme 3).<sup>42</sup> In particular, histidine derivatives such as **26** were reported to accelerate CuAAC in a similar rate than well-established DIPEA or NEt<sub>3</sub> (Figure 7).<sup>107</sup> Of note, nor imidazole or *N*-methylimidazole displayed any activating properties. Peptides are particularly challenging substrates in CuAAC since they can coordinate strongly the copper center shutting down the catalytic

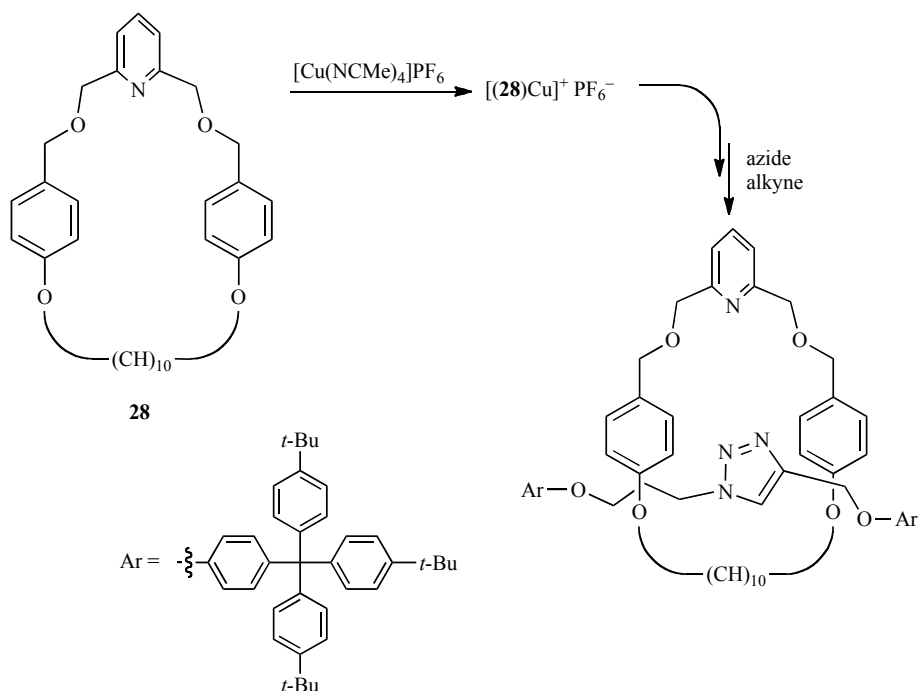
activity. However, such properties were capitalized in this work to develop self-activating cycloaddition reactions in which one of the starting materials was a histidine-containing peptide.

Other amino acids, such as proline, were also employed in CuAAC.<sup>108</sup> In particular, a proline-containing ionic liquid **27** was successfully used in the cycloaddition of *in situ* generated organic azides at 60°C under nitrogen atmosphere.<sup>109</sup> The obtained products had to be purified by column chromatography and even if the copper loadings used were rather high (10 mol %), this catalytic system could be reused in six consecutive runs without significant loss of activity.



**Figure 7.** N,O-Ligands for CuAAC

Finally, a O,N,O-containing macrocycle actively participated in the preparation of interlocked rotaxanes.<sup>110, 111</sup> In a first stage, macrocycle **28** was reacted with equimolar  $[\text{Cu}(\text{NCMe})_4]\text{PF}_6$  to yield  $[(\text{ONO})\text{Cu}]^1$  species, active in the formation of triazoles from the corresponding azides and alkynes (Scheme 6). Since the copper species remained sequestered in the resulting rotaxane no turn over was observed under these conditions. Remarkably, upon simple addition of competing pyridine, the reaction could be run with only 4 mol %  $[\text{Cu}]$ .

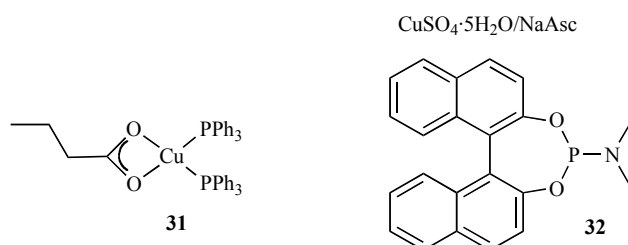


**Scheme 6.** Click preparation of rotaxanes.

### 3. Phosphorus-Based Ligands

Ubiquitous in organometallic catalysis, it is not surprising that phosphorous containing ligands, and phosphines in particular, were among the first ligands applied to the cycloaddition of azides and alkynes. In 2003, only one year after the discovery of copper(I) species as catalysts for azide-alkyne cycloadditions,  $[\text{CuBr}(\text{PPh}_3)_3]$  **29** and  $\{\text{CuI}[\text{P}(\text{OEt})_3]\}$  **30** were applied to the preparation of various glyco-derived triazoles in good yields.<sup>112</sup> One of the advantages of these catalysts is their solubility in organic solvents, allowing for the desirable homogeneous reactions for certain applications. Reactions were typically run under microwave irradiation in the presence of a base (DIPEA or DBU for the most difficult substrates). Even if no results on the absence of such additives were reported in the original study, these conditions have been widely used in diverse applications such as dendrimer construction,<sup>113-115</sup> polymer formation<sup>116</sup> or functionalization,<sup>117-119</sup> and other macromolecules such as nanotubes<sup>120</sup> or macrocycles.<sup>121</sup> Specifically, complexes **29** and **30** have been considered the catalysts of choice for the preparation of more delicate glycopolymers<sup>122-125</sup> and oligomers<sup>126</sup> or biologically active molecules.<sup>127, 128</sup> In all precedent applications a base (most often DIPEA) was employed, however, such additives were not always required and complexes **29** and **30** were active without it in the preparation of diverse glycoconjugates,<sup>129, 130</sup> polymers<sup>131</sup> or nanoparticles.<sup>132</sup>

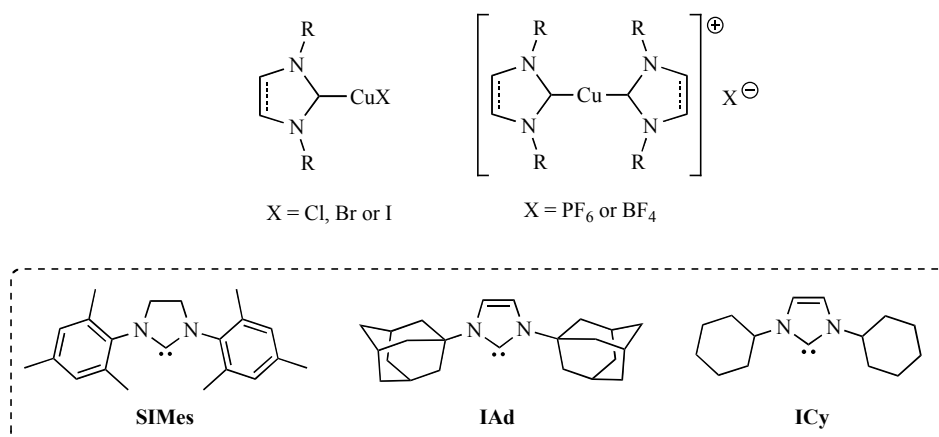
Despite the popularity of phosphorus-based ligands in modern chemistry, only two methodology studies are available so far with these species. Notably, copper(I) carboxylate complexes bearing two  $\text{PPh}_3$  ligands such as **31** were found extremely active in DCM at room temperature (Figure 8).<sup>133</sup> Under such conditions the authors could go down to 0.05 mol %  $[\text{Cu}]$  while ensuring very high yields in the corresponding triazoles. For a restricted number of substrates further reduction of the catalyst loading (down to 50 ppm) was achieved under neat conditions. Phosphoramidite ligands were also shown to accelerate CuAAC, although higher copper loadings (1 mol %) and purification on column chromatography were required when using MonoPhos ligand **32**.<sup>134</sup>



**Figure 8.** Phosphorus-based catalysts for CuAAC reactions.

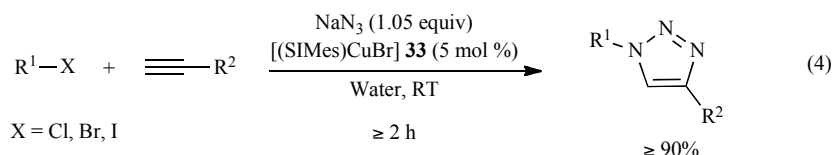
#### 4. Carbon-Based Ligands

N-Heterocyclic carbenes (NHCs), cyclic carbenes with at least one  $\alpha$ -amino substituent, have passed from laboratory curiosities to have ever-increasing applications as supporting ligands in late transition metal catalysis.<sup>135</sup> So far, two families of pre-formed  $[(\text{NHC})\text{Cu}^I]$  complexes have been studied for the cycloaddition of organic azides and alkynes, the neutral  $[(\text{NHC})\text{CuX}]$  and the cationic  $[(\text{NHC})_2\text{Cu}]X$  (Figure 9).

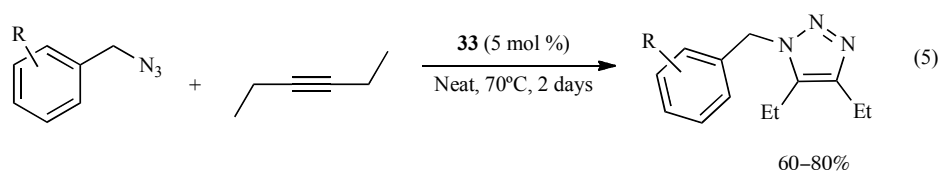


**Figure 9.** NHC-based catalysts.

The first reported NHC-containing catalyst for this cycloaddition reaction was [(SIMes)CuBr] **33**.<sup>136</sup> Less than 1 mol % of this catalyst was required for the preparation of a variety of 1,2,3-triazoles. The best solvent for this transformation was pure water, although reactions could alternatively be run under neat conditions. Notably, **33** was also active in the cycloaddition of *in situ* generated azides from the corresponding halogenated precursors, a useful strategy to avoid the isolation of organic azides particularly the ones difficult to handle. Under optimized conditions, the expected triazoles were formed in excellent yields at room temperature after short reaction times (Eq 4). These results are more impressive when compared to the conditions available in the literature at that time: 1 equiv [Cu] at 75–125°C under microwave irradiation.<sup>137</sup>

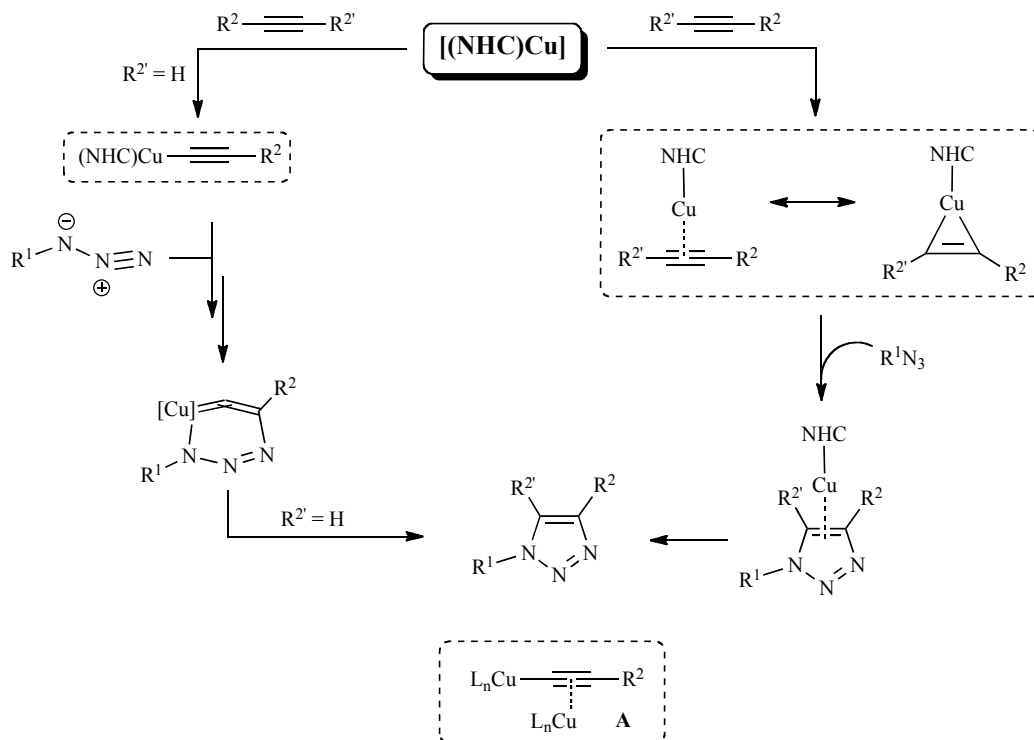


Nevertheless, the most remarkable feature of **33** is arguably to be the first copper complex reported to catalyze the cycloaddition of an azide and *internal* alkyne.<sup>136</sup> Since the first step of the widely accepted mechanism for this reaction is the formation of a copper–acetylide complex (Scheme 2), disubstituted alkynes were considered inert under such conditions. Moreover, DFT calculations had shown that a hypothetical activation toward cycloaddition *via*  $\pi$ -coordination of the copper(I) center to the alkyne has a higher energetic barrier than the uncatalyzed process.<sup>8</sup> Despite these preconceptions, different azides could react with 3-hexyne in the presence of **33** (Eq 5). Even though these reactions are not ideal, they proved the possibility of alternative activation pathways for the copper-catalyzed cycloaddition reactions.<sup>46</sup>



DFT calculations showed that the presence of a SIMes ligand on the copper center significantly promoted its  $\pi$  coordination to the alkyne, even though the  $\pi$ -bonding/backbonding contribution to the Cu–alkyne interaction was similar in the absence of the NHC ligand. Such observation led the authors to propose two

distinct reaction pathways depending on the alkyne nature. Whereas the ‘standard’ mechanism would still be applicable for terminal alkynes, the presence of an NHC on the copper center would allow for the activation of internal alkynes through a  $\pi$ -alkyne complex (Scheme 7). Of note, further theoretical studies pointed towards a significant activation in this context of copper-acetylide complexes *via*  $\pi$ -coordination of a second copper center (Scheme 7, A).<sup>138</sup>

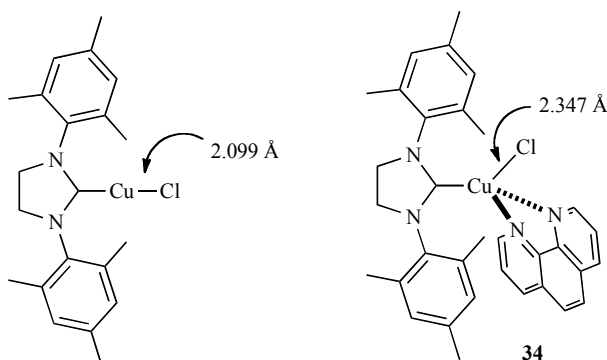


**Scheme 7.** Mechanistic proposal for [(NHC)CuX] complexes.

Despite the impressive catalytic activity of **33**, it also has some drawbacks. Notably, when the expected triazoles were oily or had a low melting-point, sluggish reactions were normally observed. Even if a higher catalyst loading (2 mol %) or reaction temperature (40°C) improved such results, a more thorough catalyst screening showed that [(IAd)CuI] was actually a better catalyst than **33** for this reaction.<sup>139</sup> Not only oily products were formed in short reaction times under identical conditions, but also [(IAd)CuI] showed a higher tolerance towards steric hindrance and group functionalities.

Alternatively, diverse variations of the SIMes-containing catalyst are currently available. Notably, a polymer-bound [(SIMes)CuCl]-derivative catalyzed the formation of 1,2,3-triazoles with only 0.2 mol % loading, even though overnight reactions led only to fair to good conversions.<sup>140, 141</sup> Moreover, aromatic nitrogen donors were reported to enhance the activity of [(NHC)Cu] species.<sup>142</sup> DMAP was found to be the best additive, however, its high toxicity precludes it from any Click reaction. Phenantroline turned out to be a good additive too and pleasantly, the authors could isolate a [(SIMes)CuCl(Phen)] **34** adduct and fully characterize it. The crystal structure of **34** showed that the copper center laid in a distorted tetrahedral environment, instead of the linear arrangement in the parent [(SIMes)CuCl] complex (Figure 10). Also, the copper–chlorine bond in **34** was significantly elongated,<sup>143</sup> which could account for the observed accelerated rates. However, direct comparison of these results with the ones with **33** cannot be

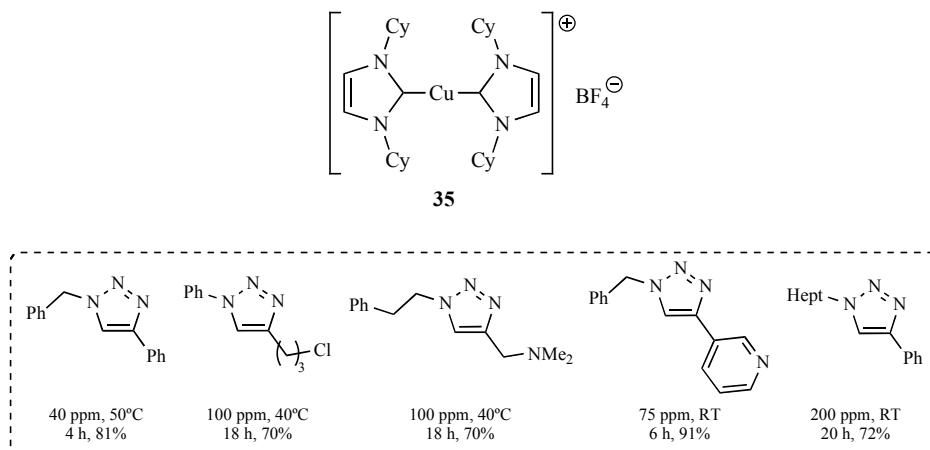
drawn at this point, since not only the halogen (Cl instead of Br) but also the solvent used (*t*-BuOH/water instead of pure water) were different in both studies.



**Figure 10.** Comparison of [(SIMes)Cu] catalysts.

Even though mainly methodological studies have been carried out so far, a number of applications are already known for neutral [(NHC)CuX] complexes, such as the development of a latent catalyst,<sup>144</sup> or the preparation of triazole-containing porphyrins,<sup>145</sup> carbanucleosides,<sup>146</sup> or chelators for platinum-based anticancer drugs.<sup>147</sup> Additionally, one major contribution of this family of complexes relies on the isolation of a NHC–Cu–triazolide complex, one of the postulated intermediates for this reaction.<sup>148</sup>

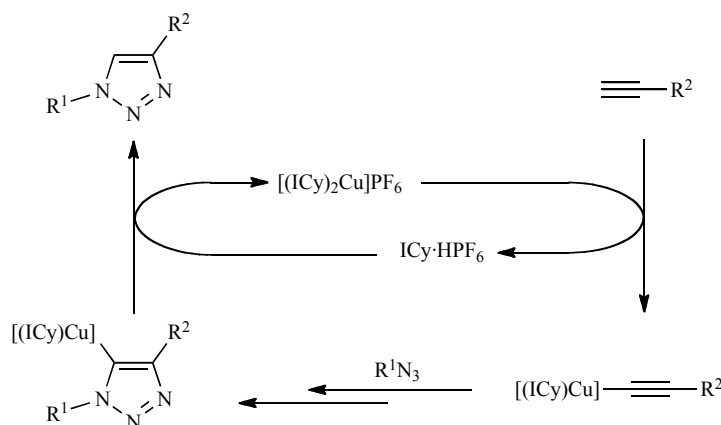
As for cationic [(NHC)<sub>2</sub>Cu]X complexes, ICy ligands were optimal in this family for ensuring excellent yields in short reaction times in MeCN or under neat conditions.<sup>149</sup> Most remarkably, extremely low catalyst loadings, down to ppm levels, were achieved with [(ICy)<sub>2</sub>Cu]BF<sub>4</sub> **35**, which translated into turnover numbers above 20000 and turnover frequencies above 5000 h<sup>-1</sup>, unprecedented for this transformations (Figure 11).



**Figure 11.** Low catalyst loading experiments.

Mechanistic studies on this system showed that whereas there was no interaction between **35** and organic azides, the copper complex was consumed in minutes in the presence of a terminal alkyne. Actually, one of the NHC ligands can act as a base and deprotonate the alkyne to initiate the catalytic cycle. The formed azolium salt was then postulated to deliver a proton to a triazolide intermediate to generate the reaction product and close the catalytic cycle (Scheme 8). Even if represented as a mononuclear mechanism, bi- or poly-nuclear pathways cannot be excluded at this point.





**Scheme 8.** Mechanistic proposal for  $[(\text{NHC})_2\text{Cu}]\text{X}$  complexes.

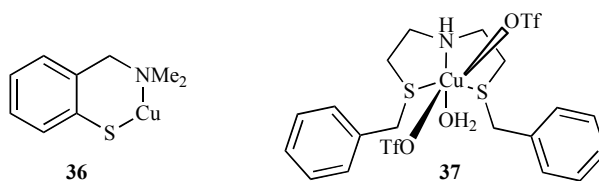
Finally, it is important to note that different studies on cycloaddition reactions of azides and alkynes have been carried out in imidazolium-based ionic liquids.<sup>150-152</sup> Even if the formation of a NHC–copper complex with the reaction media was not evoked, it cannot be ruled out neither, particularly in the presence of a base.

## 5. Sulfur-Based Ligands

Sulfur-containing ligands are the least studied ones among the families examined so far. Still, they have already shown high potential in CuAAC, even with particularly challenging substrates. In a first instance,  $\text{CuBr}\cdot\text{SMe}_2$  was simply used as a copper source soluble in organic solvents, similarly to  $[\text{Cu}(\text{NCMe})_4]\text{PF}_6$ , and applied to the production of metal-adhesive polymers<sup>153</sup> or triazoles-linked analogues of DNA.<sup>154, 155</sup> Fu *et al.* first investigated the applicability of different ligands containing at least one sulfur atom, such as dimethylsulfide, dimethylsulfoxide or thiophene, to find out that thioanisole was the most effective ligand of the series.<sup>156</sup> Moreover, the combination  $\text{CuBr}/\text{PhSMe}$  was found optimal when the reactions were carried ‘on water’,<sup>31</sup> in the absence of any organic co-solvent. Under these conditions, reactions were completed at room temperature in short reaction times. However, high catalysts loadings (10 mol %  $\text{CuBr}$  and 50 mol %  $\text{PhSMe}$ ) were required to ensure such results.

Soon after the first reports on the use of such simple sulfur-containing compounds for the formation of triazoles, other families of ligands were tested (Figure 12). van Koten *et al.* reported that only 1 mol % of copper(I)–aminearenethilato **36** was enough to ensure the efficient formation of the expected triazoles at room temperature.<sup>157</sup> In this case, no conversion was observed in water, and the reactions were carried out in DCM instead. Regrettably, the formed triazoles had to be purified by column chromatography. It is remarkable that despite the somewhat sensitive nature of complex **36** towards oxygen, the cycloaddition reactions could still be performed with no particular precautions to exclude air, except if applied to the immobilization of pincer catalysts on azide-functionalized silica where degassed solvents and inert atmosphere were required.<sup>158</sup> On the other hand, copper(II) complex **37** has been applied to the cycloaddition reaction of an *in situ* generated azide.<sup>159</sup> Even if just a model reaction was studied, catalyst loadings down to 0.5 mol % could be used running the reactions in air in a mixture MeCN/water. In this case, how the active copper(I) species are formed remains uncertain. Even if acetonitrile is known to

promote such reduction,<sup>160</sup> the reactions also proceeded in pure water. Here again, purification by column chromatography was needed.



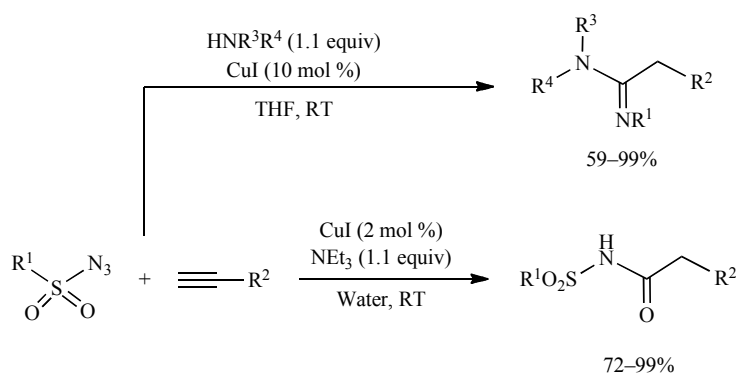
**Figure 12.** Copper complexes with sulfur ligands.

Finally, it is important to note that certain mechanistic studies on the ligand-free CuAAC were carried out in a mixture 4:1 DMSO/water.<sup>161</sup> Even if DMSO has never showed a high activity as ligand in this context, these recent results indicate that the choice of the reaction media might not be the most appropriate one, since unexpected copper ligation can occur under such conditions.

### 3. Reactivity of Electron-Deficient Azides

Sulfonyl azides have been thoroughly studied due to their rich reactivity in the presence of copper(I) acetylides. Outstandingly, the outcome of their reactions has been finely tuned with different ligands/additives in the reaction mixtures. Notably, depending on the reactions conditions not only sulfonyl triazoles, but also *N*-acylsulfonamides or azetidimines can be accessed.

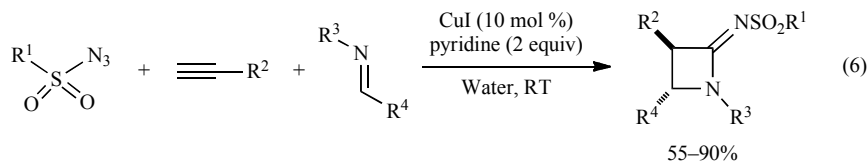
Indeed, sulfonyl azides were shown to generate amidines when reacted with alkynes and amines in the presence of 10 mol % of CuI at room temperature.<sup>162, 163</sup> Clarification of the possible different roles of the amine in this particular case remains elusive, particularly since amides were obtained instead when similar azides and alkynes were treated with CuI/NEt<sub>3</sub> in the presence of water at room temperature (Scheme 9). Whereas high catalyst loadings (20 mol %) were used when the reactions were carried out in chloroform,<sup>164</sup> only 2 mol % was enough when using pure water as solvent.<sup>165</sup> Very similar results were obtained with a combination [Cu(NCMe)<sub>4</sub>]PF<sub>6</sub>/TBTA **12** in a mixture *t*-BuOH/water at room temperature.<sup>166</sup> Furthermore, this last transformation can be regarded as an aldol-surrogate reaction since if a propargyl alcohol is employed as substrate, the resulting product would be a β-hydroxycarbonyl derivative.<sup>165</sup>



**Scheme 9.** Preparation of amidines and amides.

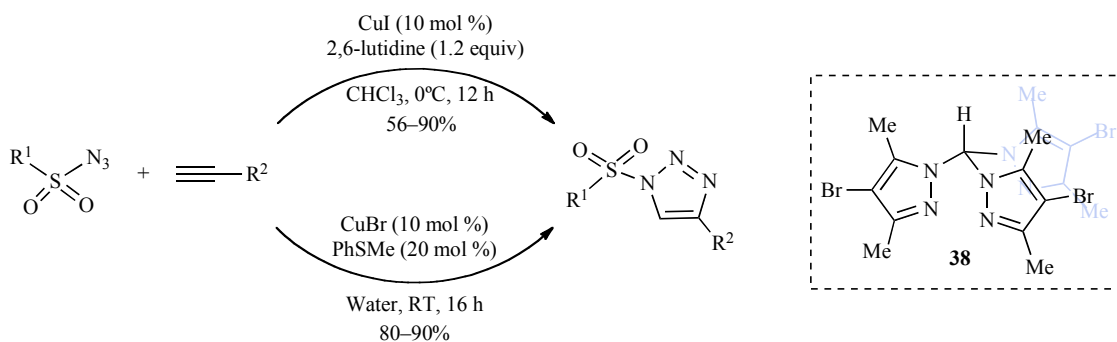
Alternatively, when the reactions were carried out in the presence of pyridine, azetidimine derivatives were isolated instead.<sup>167</sup> From the original observation, it was supposed that such derivatives were the

product of the dimerization of one of the catalytic intermediates, namely a ketenimine, thus the presence of an imine in the reaction media led to a very modular access to azatidin-2-imines under very mild conditions (Eq 6).



Furthermore, the reaction was highly selective and the *trans* isomer was in most cases the only isolated product. Interestingly, TBTA **12** also increased the rate of this reaction, but at the same time, it altered the stereoselectivity and the *cis* isomer was then obtained as the major product.

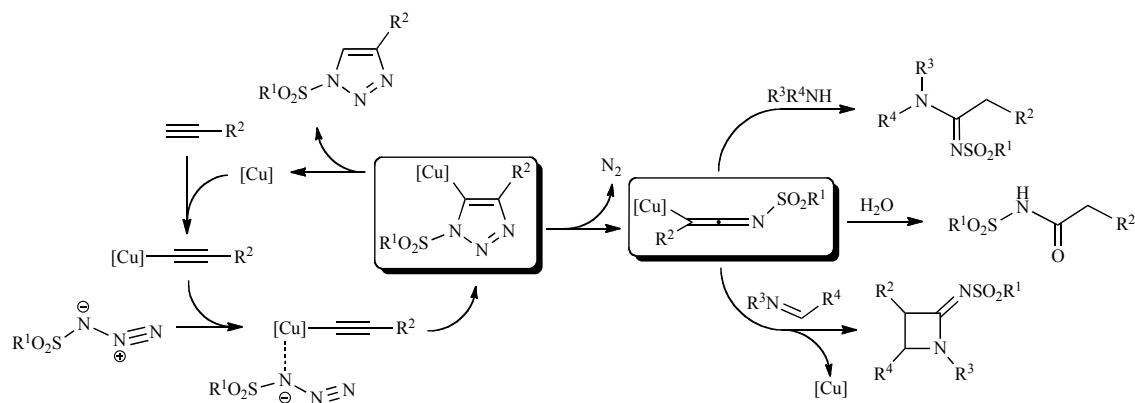
Finally, *N*-sulfonyl-1,2,3-triazoles can be obtained using a combination CuI/lutidine<sup>168</sup> or CuBr/PhSMe<sup>169</sup> after overnight stirring at room temperature (Scheme 10). It is important to note that in the absence of ligands only traces of the cycloaddition product could be detected and that no precautions to exclude oxygen were required. However, in both cases the crude triazoles need to be purified on silica gel.



**Scheme 10.** Preparation of *N*-sulfonyltriazoles.

Also, a well-defined [(**38**)Cu(NCMe)]BF<sub>4</sub> complex, where **38** is a trispyrazolylmethane ligand (Scheme 11) was used for the preparation of *N*-sulfonyl-1,2,3-triazoles.<sup>170</sup> In this case the reactions were run with 5 mol % of the copper catalyst in chloroform at 40–50°C and the reaction products had again to be purified by column chromatography.

The diverse products that can be obtained from these electron-poor azides are intrinsically related to the instability of the corresponding copper-triazolide intermediate, in which a N–N bond cleavage is particularly favored. A mechanistic rationale for the formation of the aforementioned products is presented in Scheme 11. The standard cycloaddition catalytic cycle of cycloaddition reaction of azides and alkynes would generate 1-sulfonyltriazolyl copper species, which would lead to 1-sulfonyltriazoles upon protonation. Alternatively, a ring opening process appeared to have a much lower energetic barrier than with 1-alkyl substituents. The resulting ketimines species could then be trapped with different nucleophiles, such as amine and water or imines.



**Scheme 11.** Postulated mechanisms for reactions with sulfonyl azides.

## 6. Conclusions and Outlook

The copper-catalyzed cycloaddition of azides and alkynes has certainly gained a sudden and huge popularity. The use of ligands/additives in this reaction has definitely helped to increase the impact of this transformation, but still, this cycloaddition process remains victim of its own success and only few efforts have been focused on developing efficient catalytic systems, particularly when comparing with the reports on the applicability of this process.

It is important to note that in many, if not the majority, of the applications reported so far, the reaction conditions do not completely meet the Click criteria. This fact does not dismiss the importance of such publications since often this is due to the inherent sensitive nature of the starting materials, or the products formed. Still, it is foreseeable, that a better knowledge on the effect of ligands in this reaction (notably of the mechanism and the rate limiting step) would allow for a higher number of applications to be run under strict Click conditions, with all the experimental, economical and environmental benefits this would bring.

It is curious to see that whereas for most ligands methodological studies are scarce (if any) as well as the use of pre-isolated copper(I) catalysts, their number of applications are ever-increasing. On the other hand, with NHC and sulfur-containing ligands, mainly methodological reports are available to date whereas their application to more complex systems remains mainly unexplored. Filling this gap, and gaining a better understanding of the mechanisms at play are definitely the next challenges this reaction will have to face.

### List of Abbreviations

Ad	Adamantyl [tricyclo[3.3.1.1]dec-1-yl]
Ar	Aryl
Asc	Ascorbate
ATRP	Atom transfer radical polymerization
Bn	Benzyl
Bu	Butyl
CAN	Ceric ammonium nitrate

DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DFT	Density Functional Theory
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
CuAAC	Copper(I)-catalyzed azide-alkyne cycloaddition
Eq	Equation
equiv	Equivalent
Et	Ethyl
IAd	<i>N,N'</i> -Di(adamantyl)imidazol-2-ylidene
ICy	<i>N,N'</i> -Di(cyclohexyl)imidazol-2-ylidene
Me	Methyl
MonoPhos	3,5-dioxa-4-phosphacycloheptadinaphthalen-4-yl)amine
NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
NHC	<i>N</i> -Heterocyclic carbene
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
RT	Room temperature
Ph	Phenyl
Phen	Phenanthroline
Pr	Propyl
pybox	Pyridine-bioxazoline
PMDETA	Pentamethylethylenetriamine
SIMes	<i>N,N'</i> -Bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene
<i>t</i>	<i>tert</i>
TBTA	Tris(benzyltriazolymethyl)amine
Tf	Triflate (trifluoromethanesulfonate)
THF	Tetrahydrofuran
TTTA	Tris[ <i>tert</i> -butyltriazolymethyl]amine
tren	tris(2-aminoethyl)amine
Ts	Tosyl (4-toluenesulfonyl)
<i>vs</i>	<i>versus</i>

### Acknowledgements

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