



## Digest Paper

# New click-chemistry methods for 1,2,3-triazoles synthesis: recent advances and applications

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## ABSTRACT

1,2,3-Triazoles find applications in several major technological areas, and especially in drug discovery. The click-chemistry approaches based on Huisgen's cycloaddition reaction are particularly attractive and have received enormous attention over the last decade and a half, due to their utility in preparing compounds with diverse applications, from drugs to linkers for bioconjugation.

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## Contents

Introduction	2853
Methods	2854
Generality	2854
1,5- and 1,4,5-substituted-triazole synthesis	2854
Metal-free methods	2855
Other methodologies	2856
Ultrasound	2856
Microwave	2856
Flow chemistry	2856
Click-chemistry on polymer supports	2856
Room temperature ionic liquids (RTIL)	2857
Advances and applications in medicinal chemistry	2857
In situ click-chemistry	2857
Conclusions	2858
Acknowledgments	2858
References and notes	2858

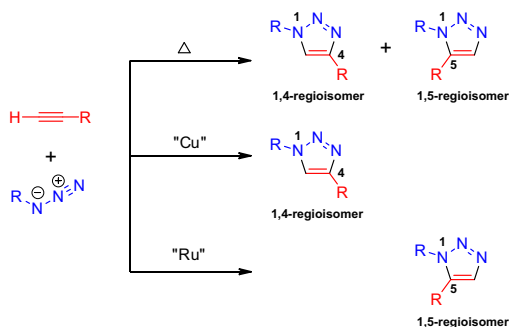
## Introduction

Over the last decade, there has been a great interest in the synthesis of 1,2,3-triazole units. Besides pharmaceutical applications,

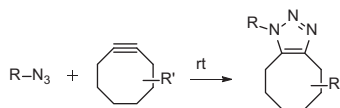
where this unit is important for biological activity, or as an amide bond isoster, it is also important in materials science and in chemical biology.<sup>1,2</sup> Huisgen was the first to study in depth the synthesis of 1,2,3-triazoles in the 1960's<sup>3</sup> giving rise to the Huisgen 1,3-dipolar cycloaddition<sup>4</sup> which involves the reaction of an alkyne and an azide to give 1,4- and 1,5-disubstituted-triazole regioisomers. In order to control the regioselectivity, several methodologies involving transition metals were developed. Originally, the copper

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**Scheme 1.** Regioselectivity of the 1,3-dipolar cycloaddition between an azide and an alkyne.



**Scheme 2.** Strain-promoted cycloaddition of azides and cyclooctynes (Cu-free click-chemistry).<sup>11</sup>

catalyzed azide alkyne cycloaddition reaction (abbreviated to Cu-AAC), developed independently by Sharpless<sup>5</sup> and Meldal<sup>6</sup> allowed the regioselective formation of the 1,4-regioisomer, whereas the ruthenium catalyzed cycloaddition gave the 1,5-regioisomer (Scheme 1).<sup>7,8</sup>

Several methodologies were then investigated to control the regioselectivity and to improve the reaction conditions for the formation of 1,2,3-triazoles. The Cu-AAC is the most well documented, with several published reviews describing the different catalysts and ligands used, including the mechanistic aspects.<sup>9,10</sup> To date several examples of the use of this click-chemistry reaction have been reported in the fields of medicinal chemistry and chemical biology. A recent example of this reaction as a bioorthogonal ligation is the strain-promoted variant developed by Bertozzi's group for cell labeling applications (Scheme 2).<sup>1,11</sup> Functionalized cyclooctynes conjugated to biotin or fluorophores react with azide labeled glycoproteins on the cell surface to give triazoles via a Cu-free click-chemistry process.

Their metal chelating properties were also recently studied by Struthers et al.<sup>12</sup> They behave as stabilizing ligands for a wide range of metals (like Pd, Cu, Zn, etc.)<sup>12,13</sup> in catalysis, including application as radiopharmaceuticals. In this digest we will focus on recent advances in their synthesis and drug discovery applications.

## Methods

### Generality

The copper catalyzed 1,3-dipolar cycloaddition between an azide and an alkyne (Cu-AAC) is the most widely used click-chemistry method due to its simplicity and high selectivity.<sup>5</sup> Its mechanism has been studied in depth.<sup>14,15</sup> The standard conditions use Cu(I) or Cu(II) salts with a reducing agent in organic solvent or a mixture of water and *tert*-butyl alcohol at room temperature. Sharpless and co-workers demonstrated the in situ preparation of the catalyst by reduction of Cu(II) salts was actually more efficient, less costly and cleaner than Cu(I) salts. Kuang et al. reported non-reductive conditions using Cu(OAc)<sub>2</sub> and by chelating the azides with *N*-containing auxiliary ligands to increase significantly the rate of the reaction.<sup>16</sup> Cu-AAC one-pot synthesis of 5-iodo-

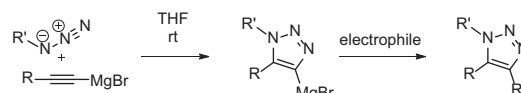
1,2,3-triazoles was also described.<sup>17,18</sup> Due to the toxicity of redox-active copper(I) species for biological applications, homogeneous silver(I) catalyst azide alkyne cycloaddition (Ag-AAC) was investigated by McNulty et al.<sup>19</sup> Silver acetate and a thermally stable phosphane ligand are used, the reaction occurs at room temperature but can be heated up to 90 °C to increase the yields. In contrast to the 1,4-disubstituted-triazoles, regioselective routes toward the formation of 1,5- and 1,4,5-substituted triazoles is not as well developed. Thus, in the last decade, efforts were made to develop new and mild methodologies for this transformation.

### 1,5- and 1,4,5-substituted-triazole synthesis

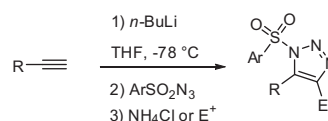
Ruthenium catalysts are the most commonly used for the synthesis of 1,5-disubstituted-triazoles from an azide and an alkyne (Ru-AAC).<sup>7</sup> Unlike the Cu-AAC process, the first described Ru-AACs supporting internal alkynes were conducted under thermal conditions, but the yields and reaction times could be improved by using microwaves.<sup>8</sup> However, this method is not efficient for sterically demanding substrates, leading to the formation of by-products, as well as requiring expensive noble metal catalysts. Krasinski et al. reported a method to give 1,5-disubstituted-1,2,3-triazoles using freshly prepared bromomagnesium acetylides at room temperature.<sup>20</sup> The reaction proceeded with good yields without any purification steps. Aliphatic acetylides were found to be less reactive than aryl ones. Further functionalization was achieved in the 4 position when a 4-halomagnesiumtriazole intermediate was trapped with an appropriate electrophile to give 1,4,5-trisubstituted-1,2,3-triazoles (Scheme 3).

More recently, lithium acetylides were used for the synthesis of 1,5-substituted sulfonyl triazoles,<sup>21</sup> which was previously performed using in situ generated copper acetylides to give the 1,4-disubstituted isomer.<sup>22</sup> The acetylenes were reacted first with butyllithium at −78 °C and then quenched with sulfonyl azide to form a triazole anion that was trapped with various electrophiles (Scheme 4). This methodology was used by Boyer for the synthesis of 1-tosyl-5- and 4,5-disubstituted-1,2,3-triazoles bearing allyl and propargylic ether appendages.<sup>23</sup>

A zinc mediated azide-alkyne version giving 1,5 and 1,4,5-substituted-1,2,3-triazoles was developed<sup>24</sup> in order to widen the substrate scope. The reaction proceeds at room temperature in the presence of a catalytic amount of *N*-methylimidazole which is required to form the zinc acetylide. In the same way as the previous methods, functionalization of the 4-position through the intermediate zinc species allowed the formation of 1,4,5-trisubstituted-1,2,3-triazoles. There was also a report on the regioselective iridium catalyzed azide-alkyne cycloaddition of electron-rich internal alkynes to give 1,4,5-trisubstituted-1,2,3-triazoles.<sup>25</sup> A samarium catalyzed cycloaddition was also described.<sup>26</sup> For example



**Scheme 3.** Synthesis of 1,5- and 1,4,5-substituted-triazoles using magnesium acetylides.<sup>20</sup>



**Scheme 4.** Synthesis of 1,5-substituted sulfonyl triazoles using lithium acetylides and sulfonyl azides.<sup>21</sup>

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