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Ruthenium catalyzed azide-alkyne cycloaddition: A review

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ABSTRACT

In recent years, there has been an ever-increasing need for rapid reactions that meet the three main criteria of an ideal synthesis: efficiency, versatility, and selectivity. Such reactions would allow medicinal chemistry to keep pace with the multitude of information derived from modern biological screening techniques.1,3-dipolar Cycloaddition reactions have emerged as one of the important type of cycloaddition reactions from the view point of chemical and biological industry. One major shortcoming of the Cu-catalyzed cycloaddition is the need for a highly toxic Cu(I) as well as Cu(II). Even in small amount, copper can damage proteins. Thus, Ruthenium catalyzed Azide-Alkyne Cycloaddition (RuAAC) for conducting the catalysis in a much convenient manner than Cu. The success with RuAAC can lead to new vistas which may be helpful in diagnostics, medical and pharmaceutical field. This article presents the mechanisms of Ruthenium catalyzed azide-alkyne cycloaddition and its application in bioconjugation and the recent developments.

Keywords: Cycloaddition, Ruthenium, Azide-Alkyne Reaction, Bioconjugation.

1. INTRODUCTION

"Click Chemistry" is a term that was introduced by Nobel Laurette Prof. K. B. Sharpless in 2001.

Click chemistry is a modular approach that uses only the most practical and reliable chemical transformations. Click Chemistry describe reactions that are high yielding, wide in scope, create only byproducts that can be removed without chromatography, stereospecific, simple to perform, and can be conducted in easily removable or benign solvents. This concept was developed in parallel with the interest within the pharmaceutical, materials, and other industries in capabilities for generating large libraries of compounds for screening in discovery research. Huisgen's dipolar cycloaddition of organic azides and alkynes is the most direct route to 1,2,3-triazoles. [1] However, because of the high activation energy (ca. 24-26 kcal/mol), these cycloadditions are often very slow even at elevated temperature (80-120 degree celcius for 12-24 h) and produce mixtures of regioisomers. The discovery that Cu(I) efficiently and regiospecifically unites terminal alkynes and azides, providing 1,4-disubstituted 1,2,3-triazoles under mild conditions, was a welcome advance. [2] Perhaps the most powerful click reaction [3] to date, the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) has quickly found many applications in chemistry, biology, and materials science. [4]

1.1. Ruthenium catalyzed azide-alkyne cycloaddition (RuAAC)

CuAAC does not afford selective access to the complimentary regioisomers of 1,4-disubstituted 1,2,3-triazoles. Although 1,5-disubstituted triazoles and 1,4,5-trisubstituted triazoles can be synthesized by the reaction of bromomagnesium acetylides with organic azides [5], this method lacks the scope and convenience of the CuAAC process. What is needed is a process for synthesizing 1,5-disubstituted triazoles and 1,4,5-trisubstituted triazoles by a ruthenium-catalyzed "fusion" of organic azides with alkynes. Catalytic transformations of alkynes mediated by ruthenium complexes are well known, and evidence for the intermediacy of ruthenium (II) acetylide, vinylidene and ruthenametallacyclic complexes has been provided. [6-8]

A search for catalysts revealed that pentamethylcyclopentadienyl ruthenium chloride [Cp*RuCl] complexes are able to catalyze the cycloaddition of azides to terminal alkynes regioselectively leading to 1,5-disubstituted 1,2,3-triazoles. In addition, RuAAC can also be used with

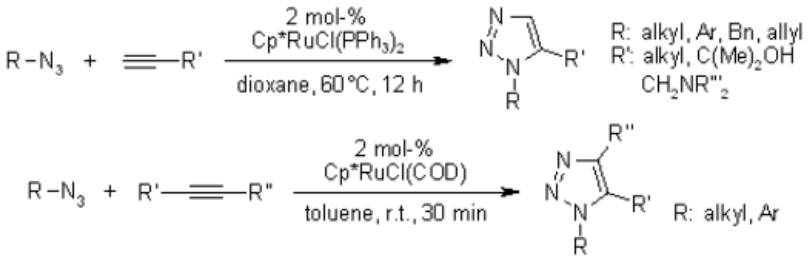

Figure 1.

internal alkynes, providing fully substituted 1,2,3-triazoles, which contrasts with CuAAC. [9]

The ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) appears to proceed via oxidative coupling of the azide and the alkyne to give a six-membered ruthenacycle, in which the first new carbon-nitrogen bond is formed between the more electronegative carbon of the alkyne and the terminal, electrophilic nitrogen of the azide. This step is followed by reductive elimination, which forms the triazole product. DFT calculations support this mechanistic proposal and indicate that the reductive elimination step is rate-determining.

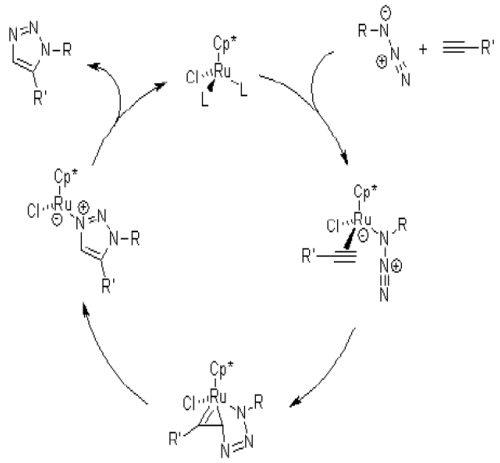

Figure 2.

The catalytic activity of a series of ruthenium(II) complexes in azide-alkyne cycloadditions has been evaluated. The [Cp*RuCl] complexes, such as Cp*RuCl(PPh 3) 2, Cp*RuCl(COD), and Cp*RuCl(NBD), were among the most effective catalysts. In the presence of catalytic Cp*RuCl(PPh 3) 2 or Cp*RuCl(COD), primary and secondary azides react with a broad range of terminal alkynes containing a range of functionalities selectively producing 1,5-disubstituted 1,2,3-triazoles; tertiary azides were significantly less reactive. Both complexes also promote the cycloaddition reactions of organic azides with internal alkynes, providing access to fully-substituted 1,2,3-triazoles. [10]

Substantial progress in ruthenium-catalyzed cycloadditions of organic azides and alkynes are reported. The catalytic activity of the ruthenium complexes and regioselectivity of the catalytic reactions were found to be dependent on the ligand environment around ruthenium. The Cp*RuCl complexes such as Cp*RuCl(PPh3)2, Cp*RuCl(COD) and Cp*RuCl(NBD) are effective at promoting the [3+2] cycloaddition. Under the influence of Cp*RuCl(PPh 3)2 and Cp*RuCl(COD), alkylazides readily react with terminal alkynes to give selectively 1,5-disubstituted triazoles. The catalytic reactions proceed easily at room temperature. The present Cp*RuCl system can also catalyze the reactions of alkylazides with internal alkynes to provide 1,4,5-trisubstituted triazoles. However, the catalytic activity could be deactivated due to the formation of catalytically inactive tetrazene complexes.

2. Applications and recent developments

The five-membered nitrogen heterocyclic 1,2,3-triazoles have attracted considerable attention in all fields of chemistry, ranging from synthetic organic/inorganic chemistry to pharmaceutical science. Among the numerous methods for 1,2,3-triazole synthesis, azide-alkyne cycloadditions involving Cu [11,12] and Ru [1]3 catalysis are most efficient ones and they have been widely used for the construction of 1,4- and 1,5-disubstituted 1,2,3-triazoles, respectively.

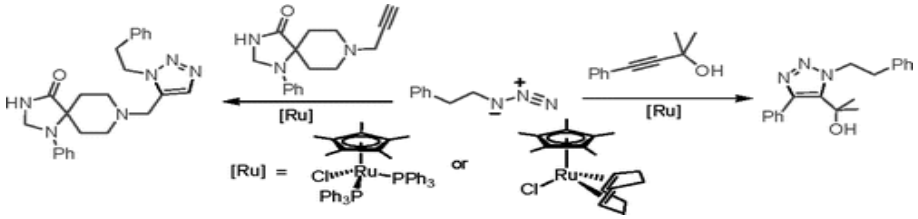

Figure 3.

Some Cp*Ru(II) complexes [13-16] and the cluster $(Cp^*Ru)_n$ in DMF under microwaves [15] are excellent metal catalysts to regioselectively assemble 1,5-disubstituted 1,2,3-triazoles. As schematically outlined in figure 4, the coordination of the starting materials onto the Ru center (step A) produces the Ru intermediate that most certainly undergoes oxidative coupling of the azide and alkyne to give the 6-membered ruthenacycle (step B), which controls the regioselectivity. The next formation of the C-N bond would then occur by reductive elimination yielding the 1,5-disubstituted 1,2,3-triazole, possibly via the coordinated heterocycle (step C). Fokin's group has reported DFT calculations supporting these mechanistic details [13]. Disubstituted alkynes work as well as terminal alkynes in this RuAAC "click" reaction, whereas only terminal alkynes give the 1,4-disubstituted 1,2,3 triazoles upon Cu-catalysis (CuAAC), because of the required terminal alkyne deprotonation giving a Cu-alkynyl species as an initial step of the latter reaction. The recovery of the Ru catalyst, however, remains a long-standing problem. Viewing economy and environmental benefit, it is essential to develop investigations of the suppression of heterogeneous Ru contamination by Ru(II) complexes upon Ru separation following the synthesis of 1,2,3-triazoles.

Dong Wang and Didier Astruc in 2014 has reported the first example of MNP-supported $Cp^*(PPh3)_2Ru(II)$ catalyst for azide-alkyne cycloaddition (AAC)[11]. The Si(OMe)3-functionalized $Cp^*(PPh3)_2Ru$ complex was obtained via coordination of Si(OMe)3-functionalized PPh3 with the (Cp*RuCl2)n cluster. Subsequently, core-shell γ-Fe2O3@SiO2 nanoparticles with an average size of 30 nm were successfully enriched with 17 by coupling reaction. This catalyst was initially evaluated in AAC using phenylacetylene and benzyl azide as model substrates with 2 mol% [Ru] in THF. The corresponding 1,5-disubstituted 1,2,3-triazole was synthesized in 91% yield and over 99.9% selectivity within 3 h. Then, the catalyst was easily removed from the reaction medium by magnetic attraction and recycled at least five times with a gradual slight loss of activity (down to 77%), and a slight decrease in selectivity for the 1,5-disubstituted 1,2,3-triazole product. The substrate scope was then investigated using aryl, aliphatic, and ferrocenyl acetylenes that exhibited good reactivities with benzyl azide in the presence of 18. The aliphatic azides and benzyl azides bearing a Br substituent are also suitable cycloaddition partners; when aryl azide (p-methoxyphenyl azide) was employed, the yield of 1,5-disubstituted 1,2,3-triazole was somewhat lower. The catalyst 18 was also active with internal alkynes such as 1,2-diphenylethyne, and the 1,4,5-trisubstituted 1,2,3-triazole product was obtained in 77% yield. [17]

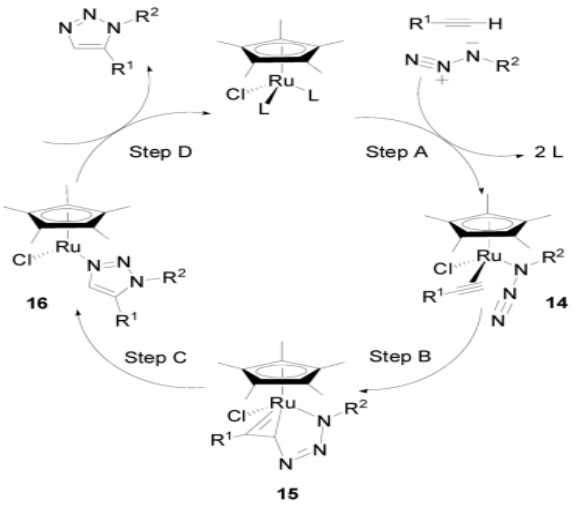

Figure 4.

2.1. Ruthenium catalyzed azide-alkyne cycloaddition in bioconjugation

Bioconjugation describes a technique in which a synthetic label (e.g. fluorophores, ligands, chelates, or radioisotopes) is covalently linked to a biomolecules (e.g. proteins and nucleic acids). Bioconjugation provides novel methods for the mild and site-specific derivatization of proteins, DNA,RNA, and carbohydrates. This stream has been developed for applications in ligand discovery, disease diagnosis, and high-throughput screening. These powerful methods owe their existence to the discovery of chemoselective reactions that enable bioconjugation under physiological conditions - a tremendous achievement of modern organic chemistry. Bioconjugation also helps in producing immobilized enzymes and certain antibodies. On the other hand, cycloaddition provides a major breakthrough in synthetic organic chemistry where the requirement of a novel product with a very simplified way of reaction is fulfilled. [18]

In 2005, ruthenium cyclopentadienyl complexes were found to catalyze the formation of the complementary 1,5-disubstituted triazole from azides and terminal alkynes, and also to engage internal alkynes in the cycloaddition (already discussed). As one would imagine from these differences, this sister process, designated RuAAC (*ru*thenium-catalyzed *a*zide–*a*lkyne *c*ycloaddition), is mechanistically quite distinct from its cuprous cousin, although the underlying activation of the alkyne component appears to be fundamentally similar: the nucleophilicity of its π-system is increased by the back donation from the ruthenium center. While the scope and functional group compatibility of RuAAC are excellent, the

reaction is more sensitive to the solvents and the steric demands of the azide substituents than CuAAC.

3. CONCLUSION

In recent years, 1,2,3-triazoles have found various valuable applications in the post-synthetic modification of functional molecules. The Cu-catalyzed cycloaddition, though, is the most widely accepted cycloaddition reaction, but it has its drawbacks due to high toxicity, which narrows its use in in-situ click chemistry. After the success with Ru, there has been a major search for the thermodynamically stable oxidation state of the metal that ranges from "0" to "+8" and also "-2". Hence, a more detailed study can be conducted in the section of Ruthenium catalyzed Azide-Alkyne Cycloaddition (RuAAC) for conducting the catalysis in a much convenient manner than Cu. The success with RuAAC can lead to new vistas to synthesizing novel and commercially viable protein conjugates which may be helpful in diagnostics, medical and pharmaceutical field as applications of RuAAC are only beginning to appear.

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