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Review Article

Ruthenium Mediated Cycloaddition Reaction in Organic Synthesis – Review

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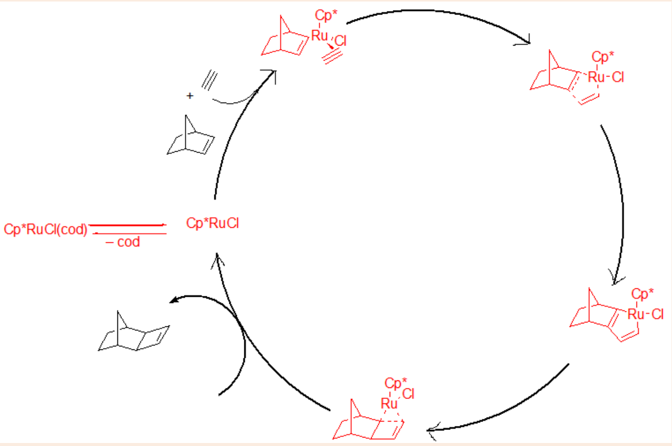
Abstract

This review is an investigation of Ruthenium catalysed cycloaddition reactions like [2+2] and [2+2+2] of alkynes and alkenes whereas [3+2] is of various azide and alkynes respectively. Click chemistry allows the assembly of new molecular entities by efficiently and reliably joining two molecular units together stably and irreversibly.



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Introduction

Ruthenium is an important transition metal which makes a number of characteristic in organic synthesis. It has a largest range of oxidation state from -2 to +8 and it allows forming a variety of ruthenium complexes. These ruthenium complexes display properties such as low redox potential, high electron transfer ability, high affinity for heteroatoms, and the ability to function as a Lewis acid. Click chemistry has Ruthenium catalyzed Azide-Alkyne Cycloaddition (RuAAC) is an important complementary method to CuAAC for regiospecific synthesis of 1, 5-substituted triazoles. RuAAC click reactions has an important role in making 1,4 and 1,5 di substituted 1,2,3-triazoles specifically in the field of heterocycles.

Ruthenium-Catalysed [2+2] Cycloadditions

In 1970, Mitshu found that the first ruthenium complex to be an effective catalyst for [2+2] cycloaddition in bicyclic olefin like norborene.The reaction conditions includes a catalytic amount of $RuH_2(PPh_3)_4$,equimolar amounts of alkyne and bicyclic alkene in benzene, a temperature of 80-100°C, and a time of 6-24 h. The highly stereo selective reactions furnished only the exo cycloadduct in modest to excellent yields depending on the alkene. After further investigation, suitable catalysts for the [2+2] cycloaddition included $RuH_2(PPh_3)_4$, $RuH_2(CO)[PPh_3]_3$, and $Ru(cod)(cot)/PBu_3$[1].For example **(Figure 1)** quantitative yields (99%) of exo adduct could be obtained in the [2+2] cycloaddition of norbornene and dimethylacetylenedicarboxylate in the presence of Ru(cod)(cot) [1].

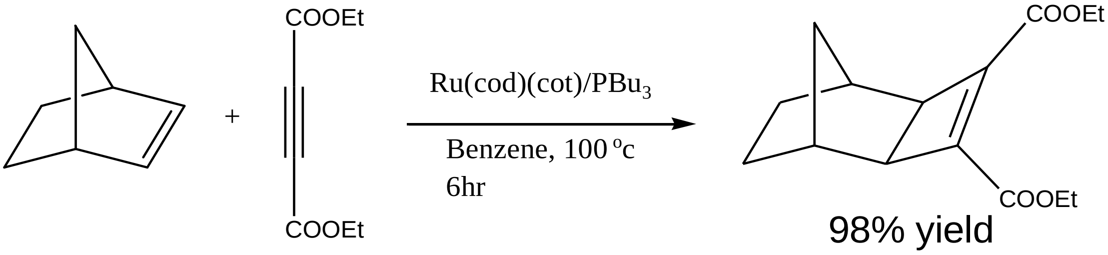


Figure 1 [2+2] cycloaddition of norbornene with dimethylacetylenedicarboxylate

Mechanism

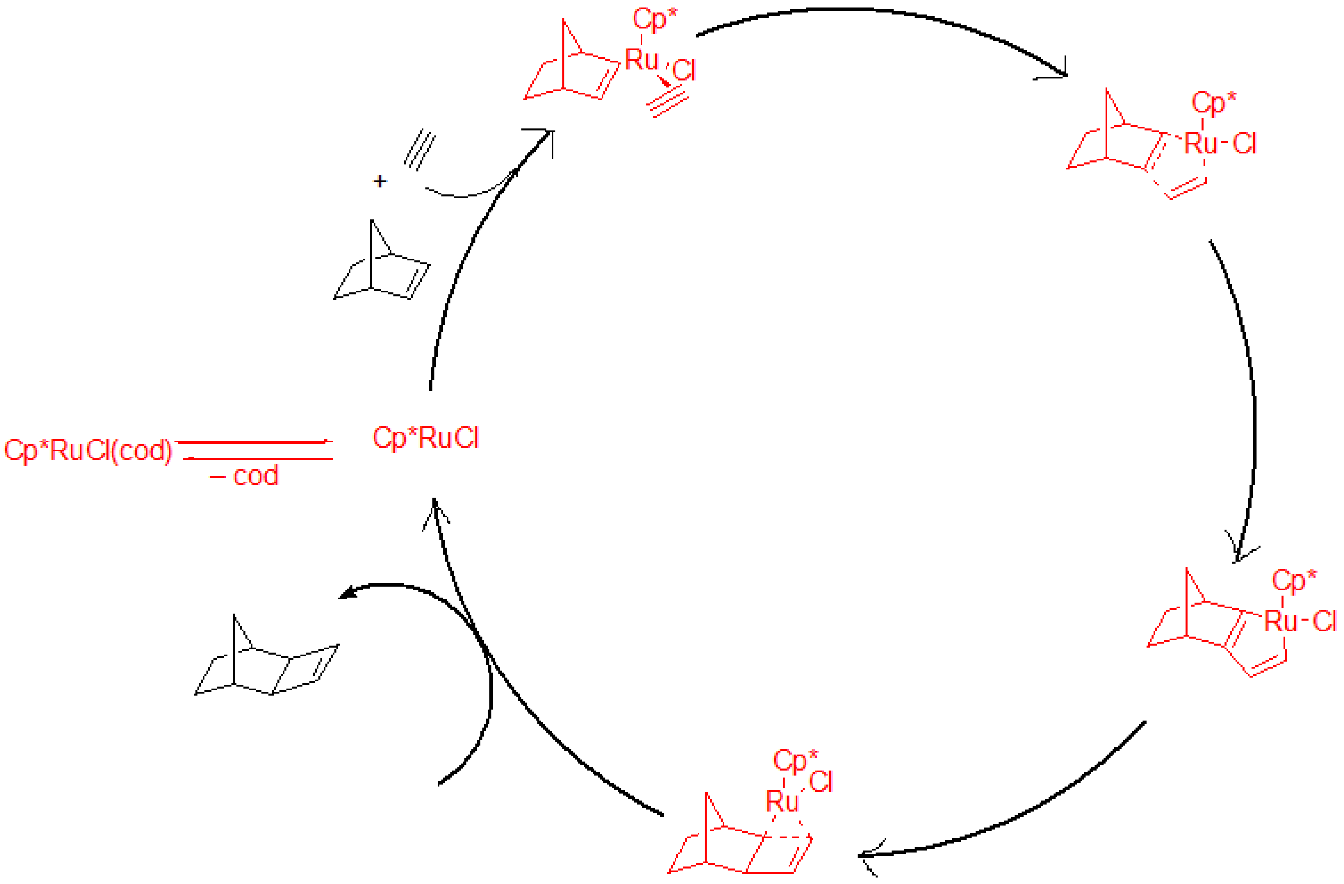


Figure 2 proposed mechanism for [2+2] cycloaddition

Ruthenium-Catalysed [2+2] Cycloadditions with Alkene-internal Alkyne

Cp*Ru(COD)Cl-catalysed [2+2] cycloadditions of norbornene and norbornadiene (**Figure 3)** with aliphatic and aromatic internal alkynes with yield of 50% to 88% [2].

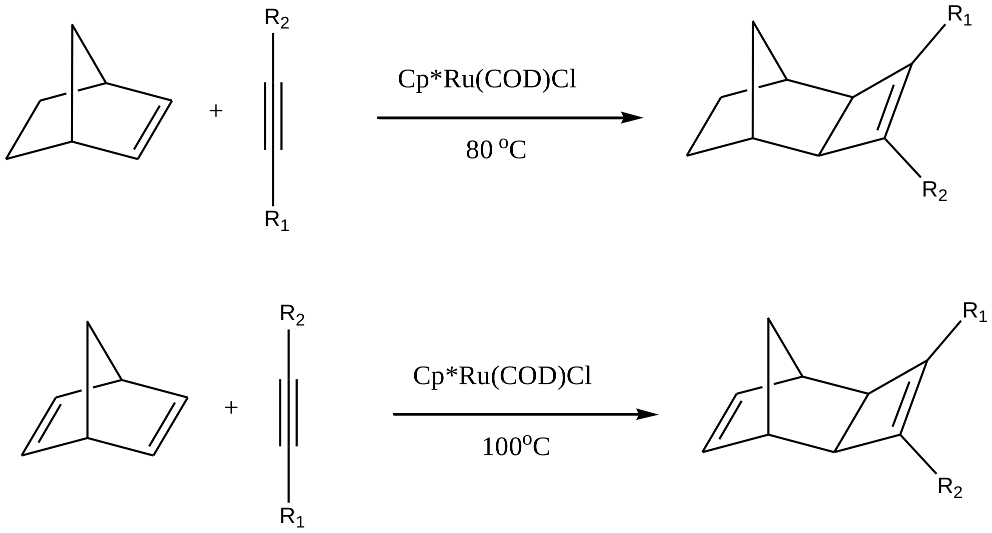


Figure 3 [2+2] Cycloadditions with alkene-internal alkyne

Ruthenium-Catalysed [2+2+2] Cycloadditions

Yamamoto *et al* reported that in the presence of a catalytic amount of Cp*RuCl(cod), 1,6-diynes chemo selectively reactedwith monoalkynes at ambient temperature to afford the desired bicyclic benzene derivatives in good yields. A wide variety of diynes and monodynes containing functional groups such as ester, ketone, nitrile, amine,alcohol, sulfide, etc. can be used for the present ruthenium catalysis. The most significant advantage ofthis protocol is that the cycloaddition of unsymmetrical 1,6-diynes with one internal alkyne moietyregioselectively gave rise to meta-substituted products with excellent regioselectivity **(Figure 4).** Completely intramolecular alkyne cyclotrimerization was also accomplished using triyne substrates to obtain tricyclic aromaticcompounds fused with 5-7-membered rings.

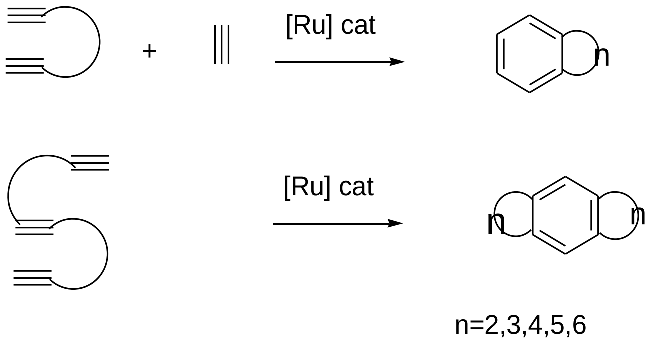


Figure 4 [2+2+2] cycloaddition with internal and external alkynes

Mechanism

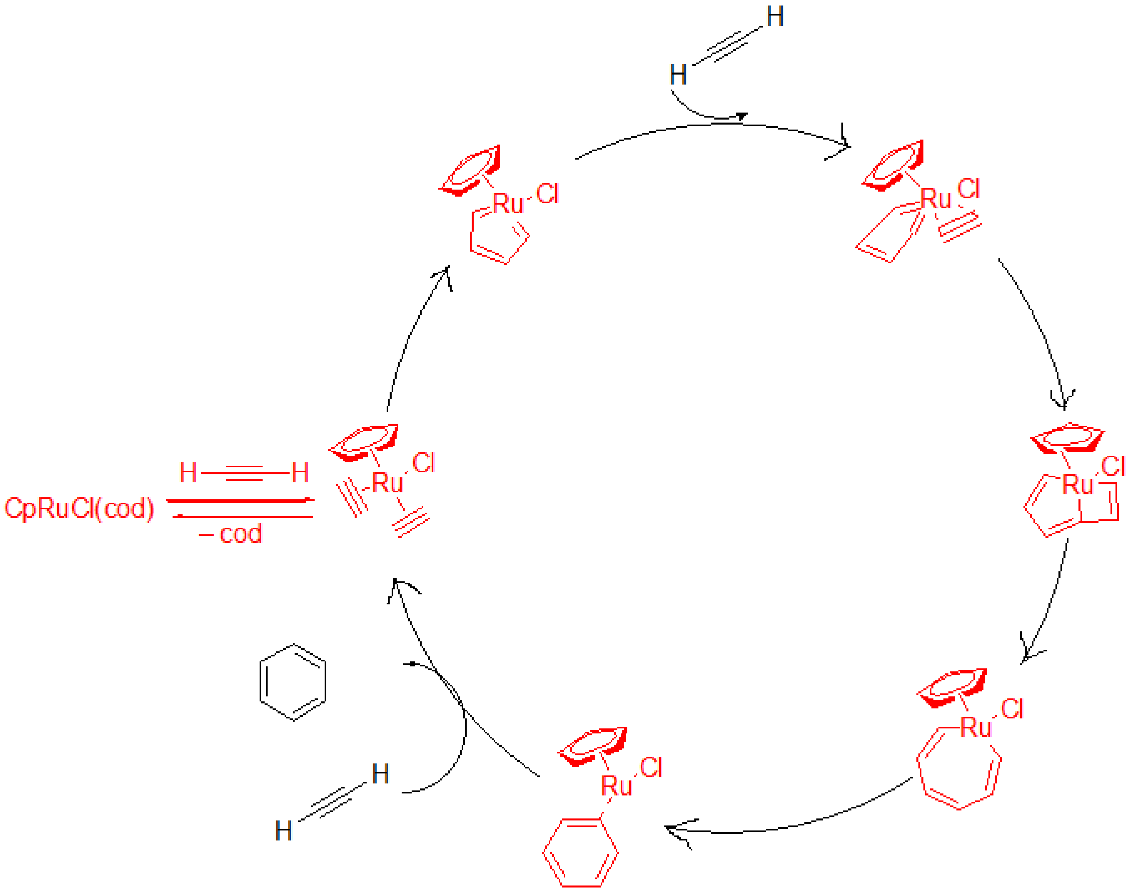
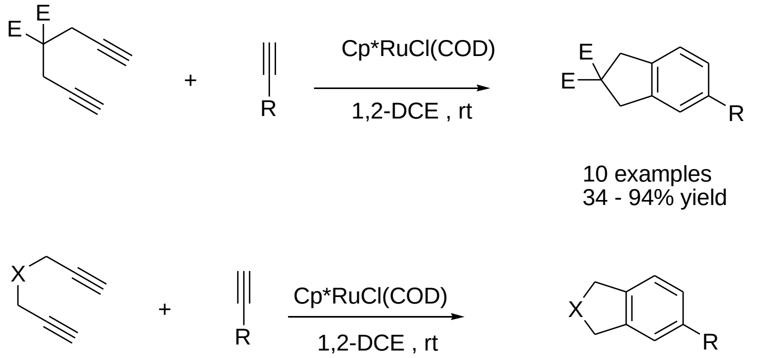


Figure 5proposed mechanism for [2+2+2] cycloaddition

Ruthenium catalysed [2+2+2] cycloaddition ofsymmetric diynes with terminal mono alkynes [3]

Ymamamoto *et al* reported the regioselective product from diynes with terminal alkynes by using ruthenium catalyst (**Figure 6**).



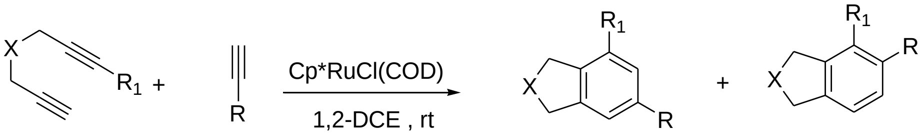
10 examples
34 - 94% yield

Where X - NTs, NBn, O and S.
5 example
60-91% yield

Figure 6 regioselective addition of diynes with terminal alkynes

Ruthenium catalysed [2+2+2] cycloaddition of unsymmetric diynes with terminal mono alkynes[3]

It formed regioselective product of meta isomer compared with ortho isomer (**Figure 7).**



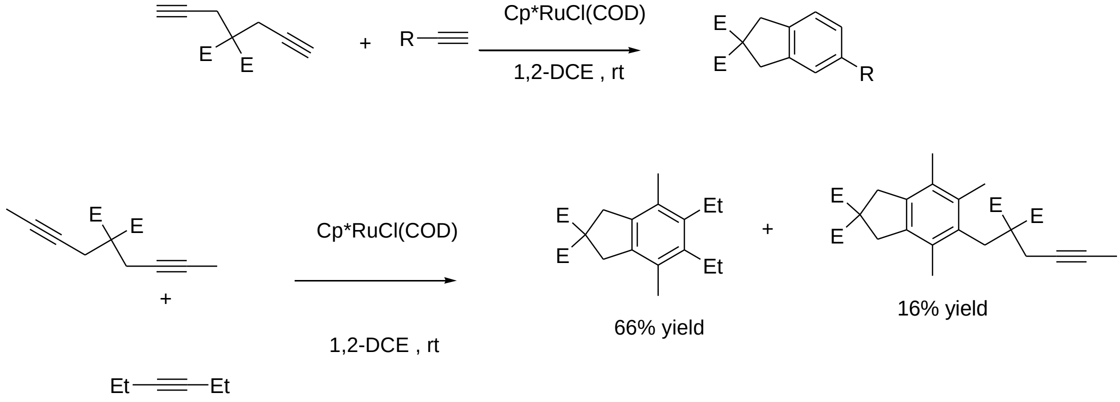
meta
major

ortho
minor

Where X - NTs, NBn, O and S.
R= H, Me

Figure 7 regioselective addition with unsymmetric alkynes

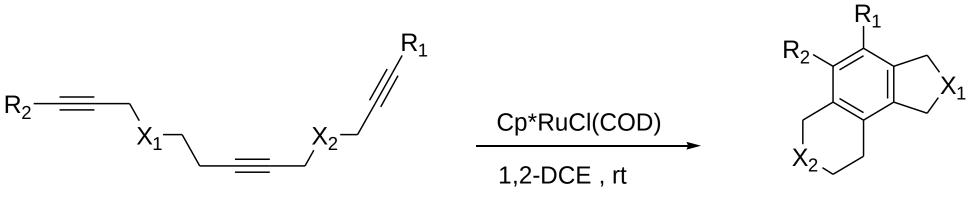
Ruthenium catalysed [2+2+2] cycloaddition of internal alkynes (Figure 8) [4]



$E=C(COOEt)_2$
R=Alkyl, Aryl
34 - 94% yield

Figure 8 cycloaddition with internal alkynes

Ruthenium catalysed cycloaddition of triynes (Figure 9)



Where X_1 and X_2 = NTs, O, S, $C(COOEt)_2$,
$R_1$and R_2 =H, Me

Figure 9 Cycloaddition with triynes

Ruthenium-Catalyzed Azide-Alkyne Cycloaddition

A short overview of the RuAAC, the most used clickreaction, is presented, including the introduction of the "click" concept, the conditions of copper(I) catalysis,the regioselectivity, the nature of the catalysts and ligands, mechanistic features, experimental conditions and applications to organic synthesis and organic materials.Although the copper-catalyzed cycloaddition of azides and terminal alkynes**(Figure 10)** to form1,4-disubstituted 1,2,3-triazoles is well-known [5].

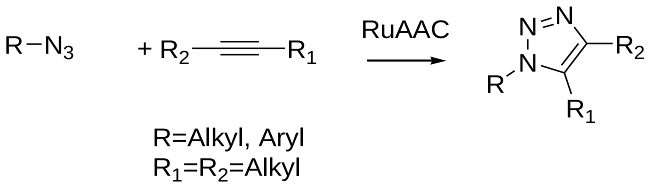


Figure 10 RuAAC general Scheme

Mechanism

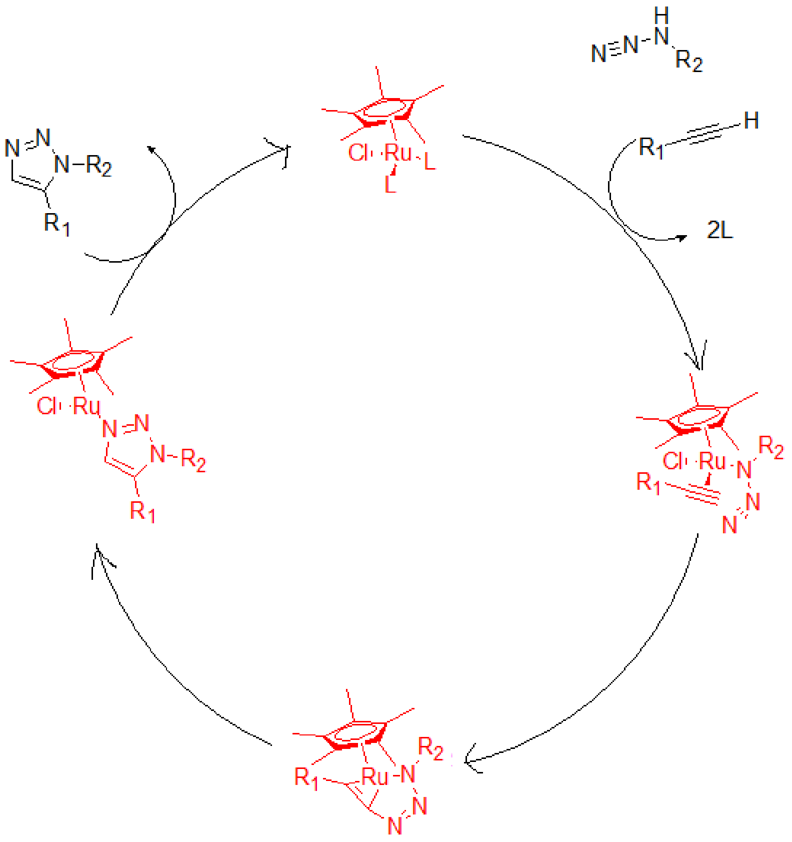
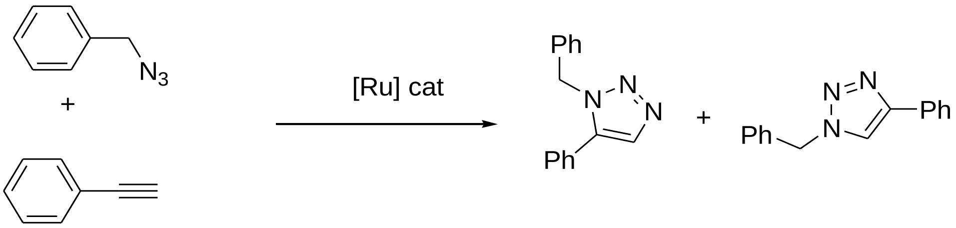


Figure 11proposed mechanism for RuAAC

Regioselective [3+2]cycloaddition terminal alkynes and azide by ruthenium complexes

Sharpless and co-workers recently reported the ruthenium-catalyzed counterpart to form the complementary 1,5-disubstituted triazoles. Whereas the Cu(I)-catalyzed reaction is typically limited toterminal alkynes, the Ru(II)-catalysed (**Figure 12& Table 1**) one takes place with internalalkynes as well [6].



1a 2a

Figure 12 reaction alkyl azide with terminal alkynes

Table 1 Complexes used to synthesizing 1, 5 and 1, 4 – disubstituted triazoles

Complex	1a	2a
$Ru(OAc)_2(PPh_3)_2$	-	100 %
Cp RuCl $(PPh_3)_2$	85 %	15 %
Cp*RuCl $(PPh_3)_2$	100 %	-
Cp*RuCl (NBD)	100 %	-

Regioselective [3+2] cycloaddition terminal alkynes and azide by ruthenium complexes with microwave irradiation

L. K. Rasmussen *et al* were performed RuAAC click reactions between aryl azides with terminal alkynes and alkyl azide with terminal alkynes by microwave irradiation. **(Figure 13)**Microwave assisted organic reaction is an emerging tool to synthesizing a number of organic compounds [7]·

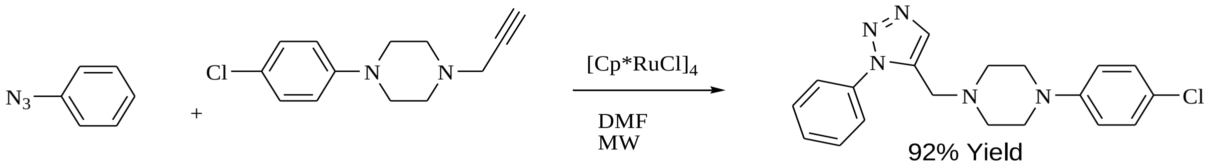


Figure 13 MW assisted azide alkyne cycloaddition

Pradere *et al*,reported for preparation of ribavirin analogues by RuAAC click reaction by using MW irradiation**(Figure 14)** with the good yield [8].

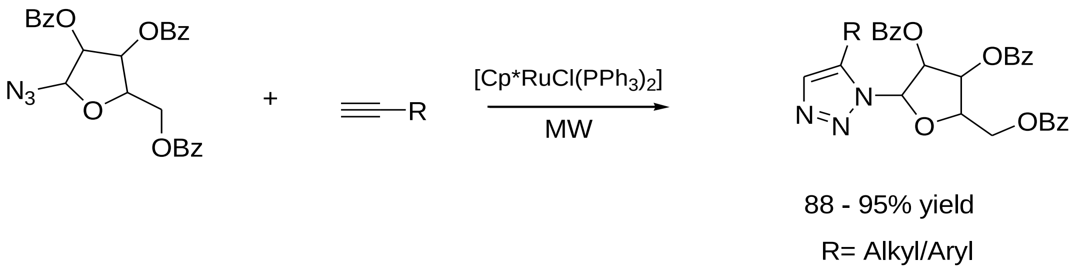


Figure 14 MW assisted RuAAC reaction in ribavirin analogues

Reaction with internal alkynes

Hou *et al*, reported that the reaction which include azide and internal alkynes (**Figure 15**) by RuAAC [9].

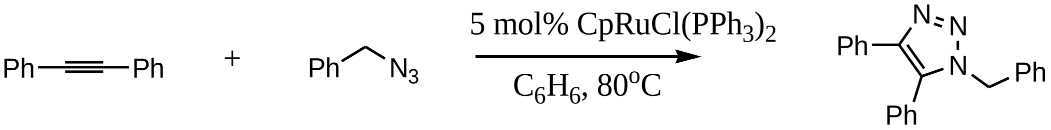


Figure 15 RuAAC with internal alkynes

Applications of click chemistry in heterocyclic compounds

Mingyan Zhu *et al* constructedthe polyheterocyclicbenzopyran library with diverse core Skeletons (**Figure 16**) through RuAAC click reactions [10].

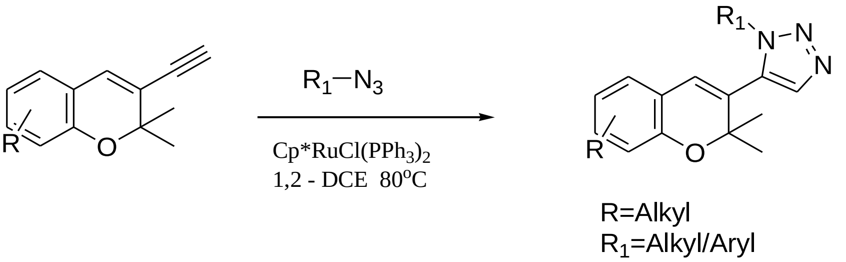


Figure 16 RuAAC in Hetrerocycles

Biet.T *et al* were synthesized the electro activetetrathiafulvalenyl-1, 2, 3-triazoles (**Figure 17**) by click chemistry [11].

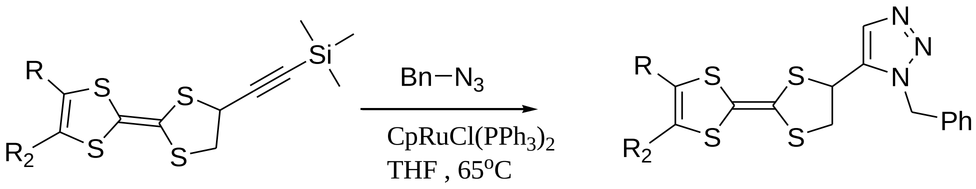


Figure 17 RuAAC thio compounds

Applications of Click chemistry in Metallocenes

Edith Chardon and co-workers explored the palladium and ruthenium complex for antiproliferative activities of the different complexes assayed against several cancer cell lines (KB, MCF7, HCT116, PC3, SKOV3,OVCAR8, HL60) and healthy cell lines (MRC5, VERO, EPC),which established their efficiency. They synthesized palladium based metallocene complex which undergo alkyne azide cycloaddition to form 1,5 disusituted 1,2,3-triazole complex**(Figure 18).** They are failed to attain the 1,4 disubstituted 1,2,3-triazolemetallocene product by CuAAC click reaction [12].

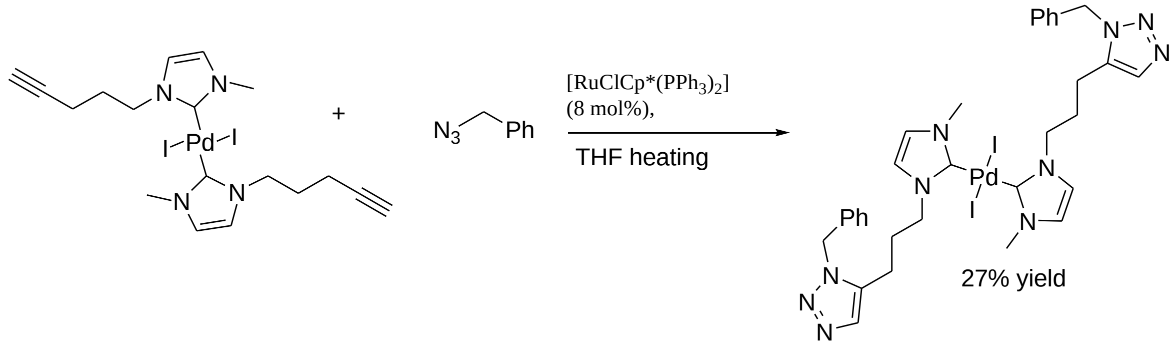


Figure 18 In metallocene

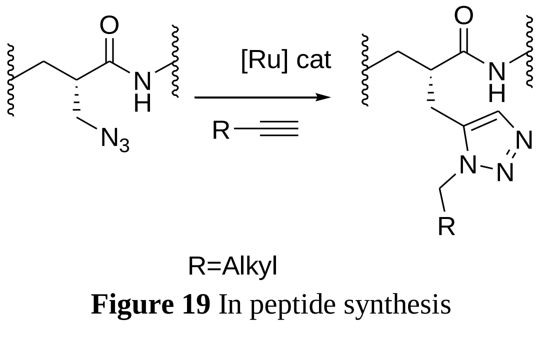
Solmon A.J *et al* synthesised metallocene-based inhibitors by using RuAAC for cancer-associated carbonic anhydrase enzymes IX and XII. Their experiments involving iron metallocene complex with ruthenium [13].

Applications of click chemistry in peptide synthesis

Pederson and Abell worked on peptidomimetic chemistry to synthesis 1, 2, 3-triazoles **(Figure 19)** peptides by using CuAAc as well as RuAACClick chemistry. They were reported that trans and cis peptides were prepared by ruthenium complex and copper complex respectively [14].

Conclusion

The brief report of Ruthenium catalysed cycloaddition including [2+2] alkene-alkyne cycloaddition, [2+2+2] alkyne-alkyne cycloadditionand [3+2] alkyne – azide cycloaddition reactions was carried out. The necessity of this review arises because of the usage of ruthenium catalysed cycloadditions reactions in a variety of ring system via diyne –monoalkyne and triyne templates. And also click chemistry has revolutionized chemical biology and will further extend our capability to engineer customized therapeutics with pharmacological properties that are optimized for each specific application of drug discovery particularly for neurodegenerative diseases, cancer, and HIV infection.



R=Alkyl

Figure 19 In peptide synthesis

Acknowledgments

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