Exploring Molecular Intricacy with Non-metathesis Couplings Catalysed by Cyclopentadienyl Ruthenium (III) tris-acetonitrile hexafluoro phosphate [CpRu(CH3CN)3]PF6^{-}

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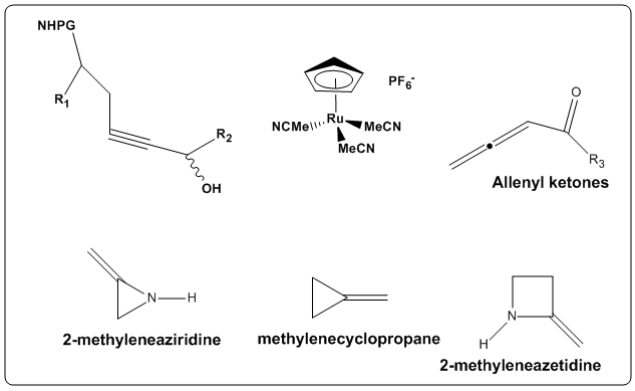
Abstract: The demand for new chemicals spanning the fields of healthcare to materials combined with the pressure to produce these substances in an environmentally benign fashion pose great challenges to the synthetic chemical community. The maximization of synthetic efficiency by the conversion of simple building blocks into complex targets remains a fundamental goal. In this context, ruthenium complexes catalyse a number of non-metathesis conversions and allow the rapid assembly of complex molecules with high selectivity and atom economy.The ability of ruthenium to assume a wide range of oxidation states (from -2 to +8) and varying coordination geometries provides unique opportunities for catalysis. These include reactions initiated by metallacycle formation, vinylidene formation, C-H activation, and activation of carbon-carbon multiple bond formations.The project would primarily focus on the studies of reactions of properly substituted N-protected propargyl alcohols and Michael acceptors in presence of the Ruthenium catalyst Tris-acteonitrile cyclopentadienyl Ruthenium(I) hexafluorophosphate [CpRu(CH3CN)3]PF6. The reactions would be further examined with Allenyl ketones, methylene cyclopropanes, methylene aziridines and azetidines. Efforts would be executed to understand the nature of products formed and the mechanism involved. Ruthenium catalysed metathesis reactions have become useful worldwide whereas the non-metathesis catalysed reactions to form carbon-carbon bonds is a relatively unexplored and new field.



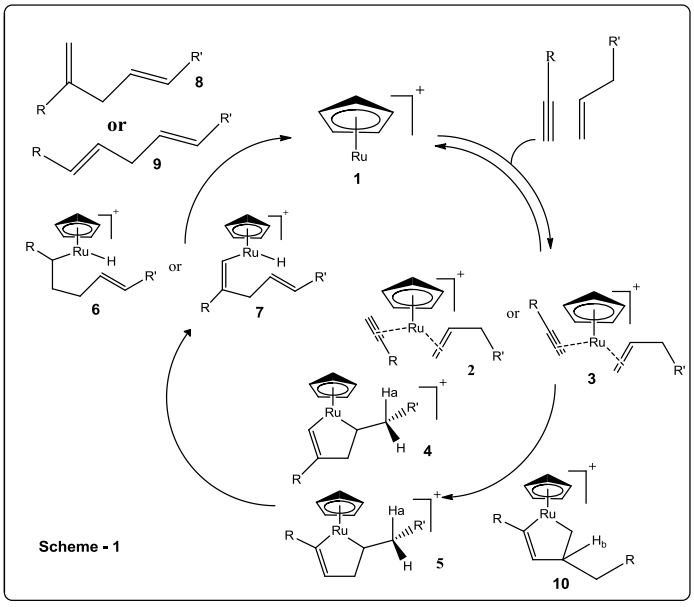
In the realm of organic chemistry, synthetic organic chemistry reigns supreme as the most fascinating area of activity. The formidable synthetic challenges imposed by the presence of highly intriguing and complex structural networks in natural products compounded by the additional presence of multiple chiral centres have brought out the ingenuity of synthetic chemists in meeting such challenges. A very useful spin-off of such efforts has also been the development of new methodologies of carbon-carbon bond formation and functional group transformations, better and more effective reagents of selectivity for above transformations which have made short-work of otherwise longdrawn synthetic sequences. The signal developments in asymmetric synthesis during the last decade have added a new dimension to

the fast changing facet of synthetic organic chemistry.

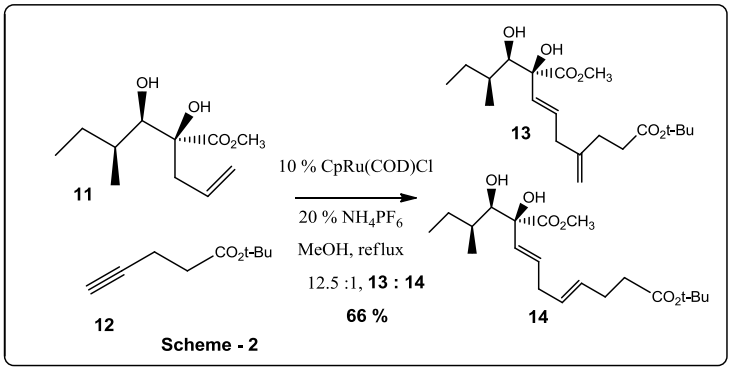
The Synthetic Scientist community has been put under increased pressure to produce, in an environmentally benign fashion, the myriad of substances required by the society. Thus green chemistry has emerged as important aspect of synthetic chemistry. A major goal of this endeavour must be to use raw materials efficiently. Thus synthetic efficiency has to be addressed not only by selectivity but also economically.[1,2]

Cationic Ruthenium **(+2)** complexes catalyse the coupling of alkynes and alkenes (an Alder –ene type reaction). A mechanism involving generation of a π-allyl ruthenium complex from activation of the alkene's C-H was originally proposed; however, it is now generally believed that the reaction proceeds via a ruthenacyclopentene.[3] The proposed reaction mechanism is shown as **Scheme 1.** After coordination of the alkyne and alkene by the coordinatively unsaturated ruthenium (+2) catalyst **(1)** to form complexes to form complexes **(2)** and **(3)**, ruthenacyclopentenes **(4)** and **(5)** are possible, depending on the orientation of the alkyne. Although, in principle, the alkene can also coordinate with the opposite orientation (to generate a ruthenacycle such as **10**), the difficulty in achieving the required geometry for *syn-β*-hydrogen elimination of H_b prevents this ruthenacycle from leading to product. Ruthenacycles **(4)** and **(5)** then undergo *syn-β*-hydrogen elimination of Ha to generate vinylruthenium (+4) hydrides **(6)** and **(7)**. Theses complexes undergo a reductive elimination to form 1,4-diene products **(8)** and **(9)** and regenerate the ruthenium(+2) catalyst **(1)**. The Alder-ene reaction of alkene **(11)** and alkyne **(12)** is catalysed by 10 % CpRu(COD)Cl and 20% ammonium hexafluorophosphate to afford 12.5:1 mixture of isomeric dienes **(13)** and **(14).**[4] Thus, the reaction generally favours carbon-carbon formation at the more substituted carbon of alkyne (the branched product) although several factors can reverse this trend.

Steric factors, especially at the propargylic position, can control the regioselectivity of the



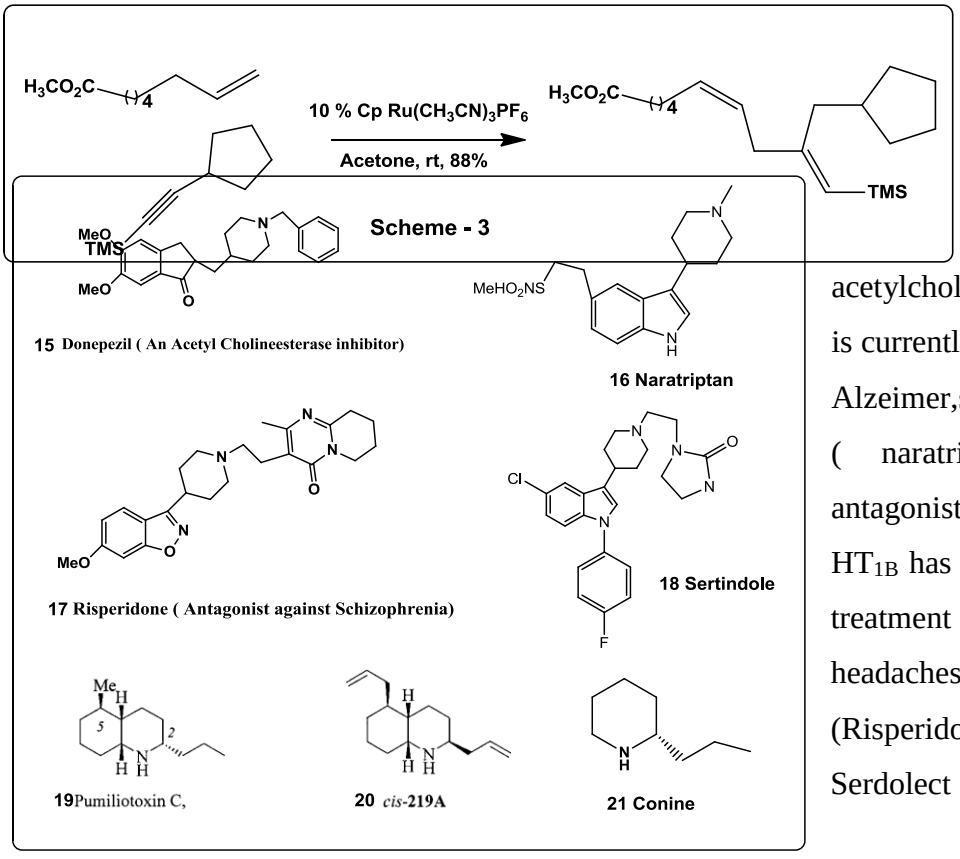
carbon carbon bond formation. In general, the ruthenium catalysed reaction of alkynes bearing a quaternary propargylic carbon or silicon results in formation of the new carbon- carbon bond distal to this quarternary carbon or silicon. For example, the ruthenium catalysed coupling of alkene and trimethylsilyl alkyne provides 1,4-diene in 88% yield as a single regioisomer. **(Scheme -2 & 3)**



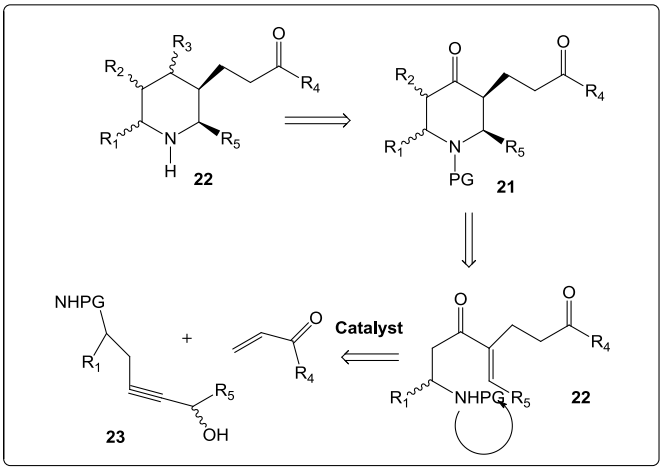
Scheme - 2

In the case of trimethylsilyl alkynes, the more reactive cationic ruthenium complex, CpRu $(CH_3CN)_3PF_6$, is used in place of the original catalyst CpRu(COD)Cl. The former catalyst also allows for the coupling of alkynes to 1,1- and 1,2-substituted alkenes, [5] both of which were unreactive when CpRu(COD)Cl was used as a catalyst. (**Scheme- 3)**

The main concern of this project is to develop an atom-economic and generalized synthetic methodology of polysubstituted piperidones employing simple starting materials because the piperidones form a central core for many pharmaceutically important natural products. [6] Aricept (**15)**, (Donepezil), an acetylcholineesterase inhibitor, is currently being prescribed for Alzeimer,s syndrome. Naramig (naratriptan) **(16)** , an antagonist of 5-HT_{1D} and 5-HT_{1B} has shown promise in the treatment of migraine headaches. Risperdal (Risperidone) **(17)**, and Serdolect **(18)**, both

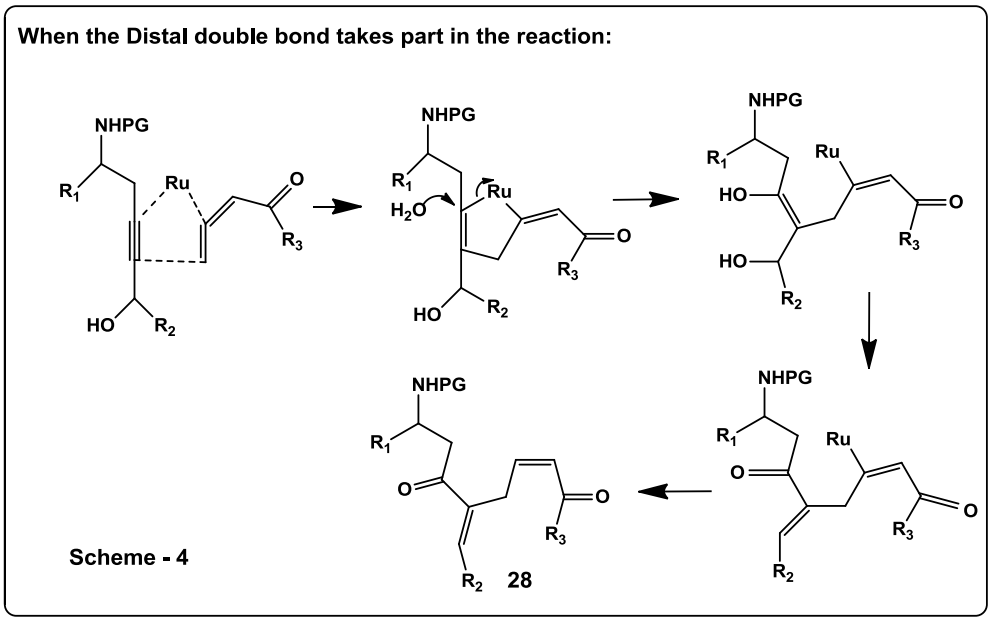


nonselective 5-HT/D2 antagonists are currently being utilized in the treatment of schizophrenia. Apart from these four, there is a huge variety of piperidine natural products with an extensive range of biological activities. A simple efficient methodology employing ruthenium catalysis is predicted to accomplish the polysubstituted piperidine system. Retrosynthetically we envisage that a well functionalized piperidine (**22**) can be achieved from reduction of a 1,4-piperidones (**21**) which can further be achieved from an intramolecular Aza-Michael type 6-*endo* addition to a α,β- unsaturated ketone by the N-protected amine (**22**). The functionalized protected amine was to be achieved from a Ruthenium catalysed conjugate addition of a propargyl alcohol (**23**) and a Michael acceptor like Methyl-vinyl ketone.

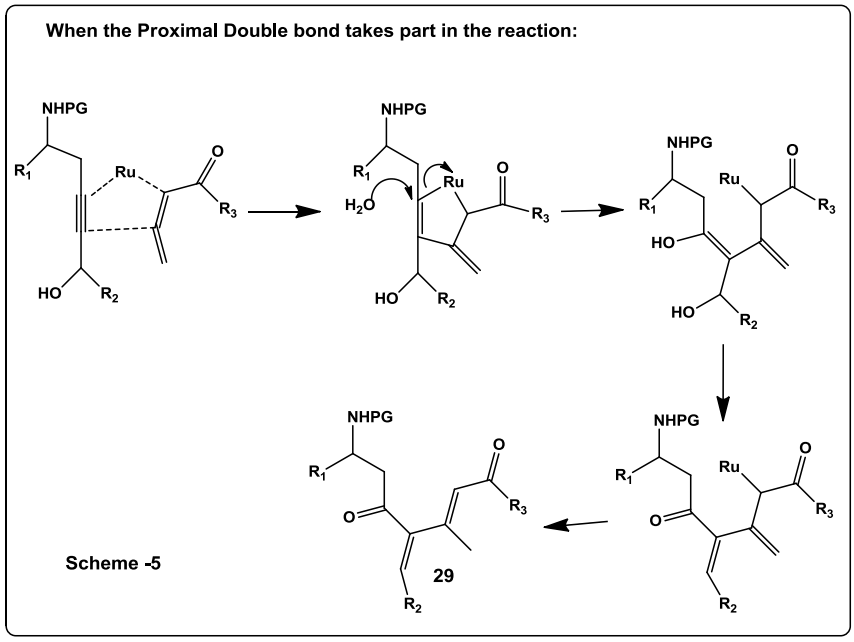


Not only the Michael acceptors, the project would also explore the mechanism involved and the products developed from non-metathesis coupling of varied substituted propargyl alcohols with allenyl ketones **(23)** , methylene-aziridines **(24)** , methylene cyclopropanes **(25)** and methylene azetidines **(26)** and 2-methylene indanones **(27).**

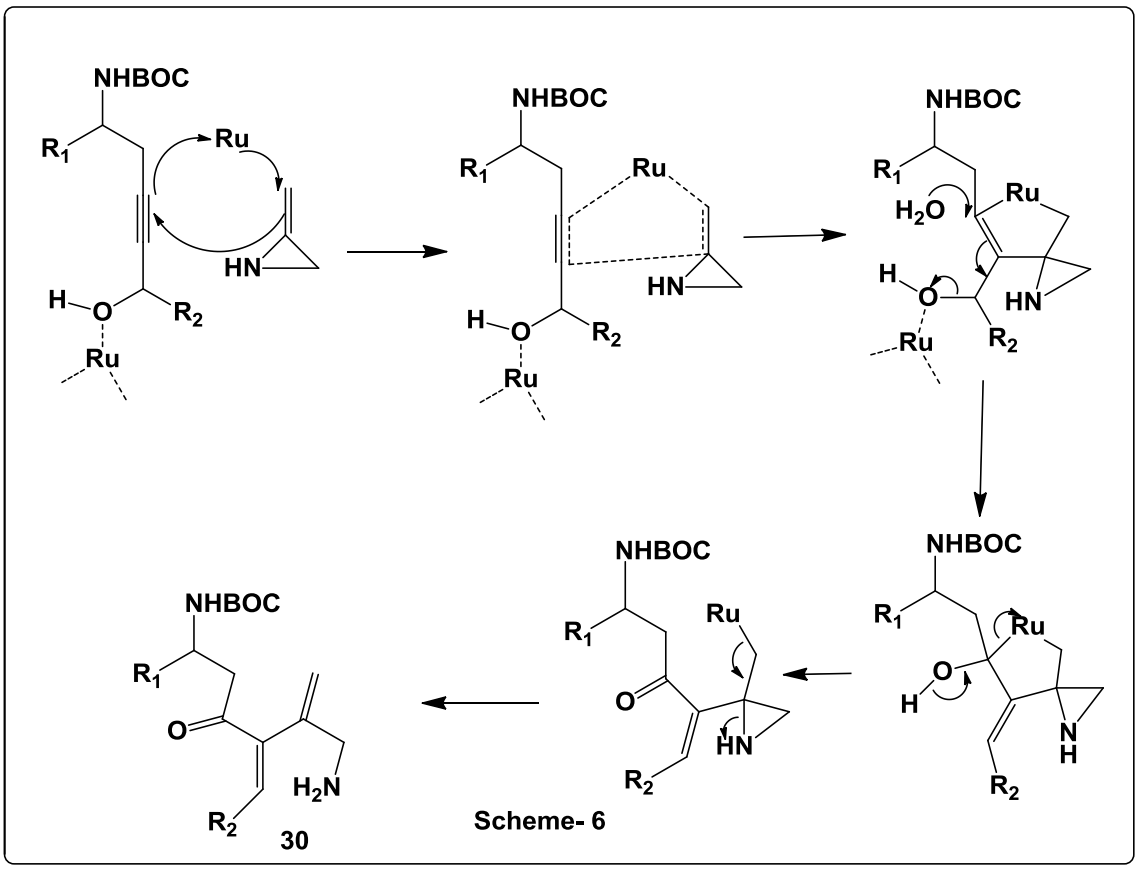
The basis for choosing such reactants with Propargyl Alcohol under Ruthenium Catalysis is purely based on the hypothesis of the products to be formed through a probable reaction mechanism in each case. The group wants to explore which bond would definitely react with the propargyl alcohol to form the Ruthenium cyclopentene formation.



Would it be regio-selective or not? This question can be of focus and a following scheme can be sketched out.The participation of the distal double bond ends up in an enone **(28)** and the proximal one to a differently substituted branched enone **(29),** both can be efficient precursors to piperidones. **(Scheme 4 and 5)**

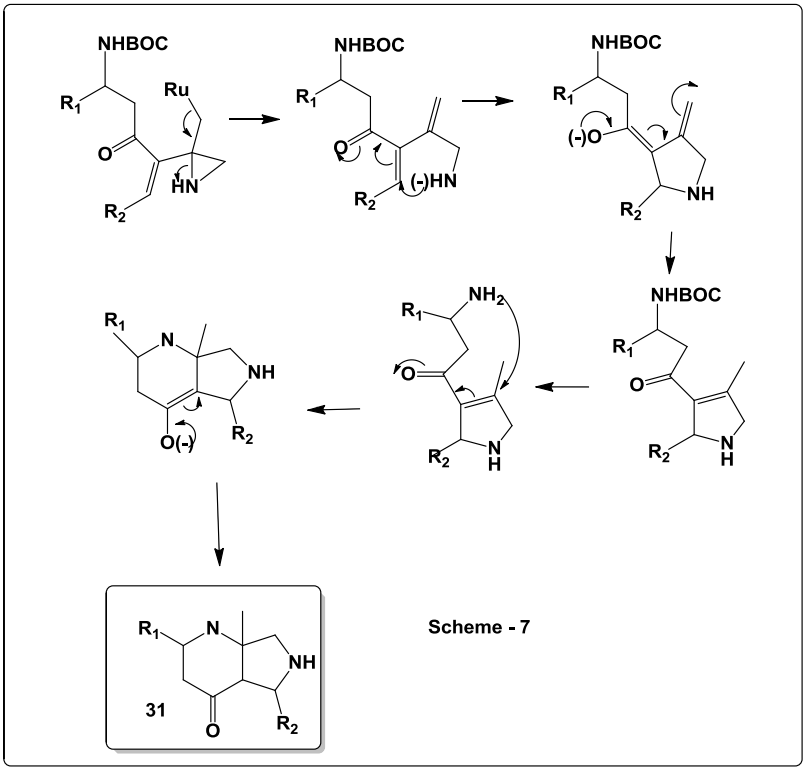


Methylene aziridines **(24)** can be fantastic precursors to such non-metathesis couplings as the reactive tricyclic system can get easily cleaved to get conjugated amines which are not easily achievable.

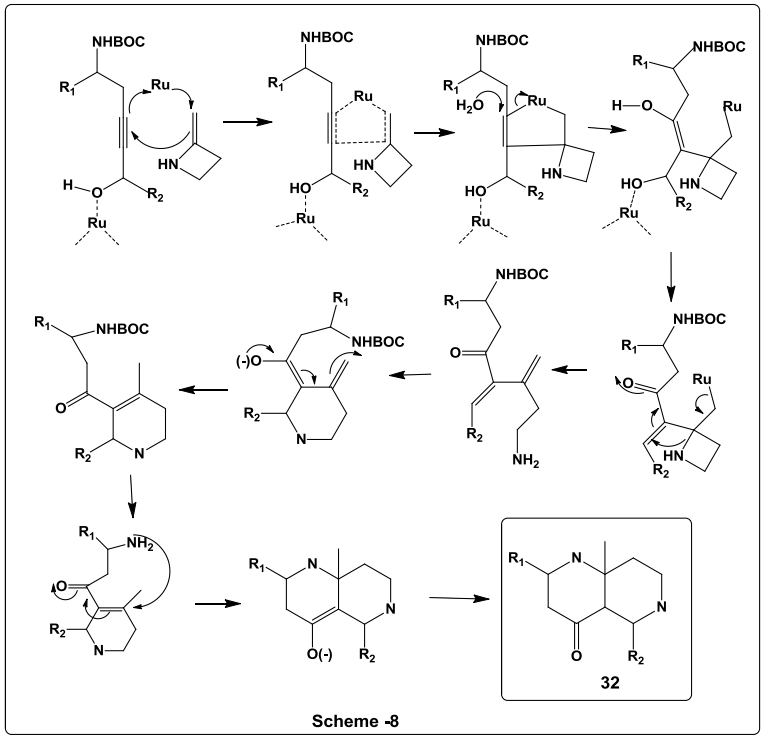


The fair chances for *in-situ 6-endo* cyclisation can also lead to a fused bicyclic piperidone **(31)** with varied functionality and substitution thus proving to be an efficient moiety for bioactive alkaloid systems. **(Scheme-7)**

In similar fashion, methylene azetidines **(26)** can also be suitable precursors to such diverse acyclic and cyclic nitrogen systems. The bicyclic piperidone **(32)** with two secondary nitrogen atoms at 1,5 position cannot be easily achieved in such an one-pot synthetic protocol. Such mixture receipes of propargyl alcohols and reactive moieties like methylene cyclopropanes **(25)** and methylene Indanones **(27)** can be other interesting sites of new discoveries in Ruthenium catalysis which definitely needs to thoroughly explored.

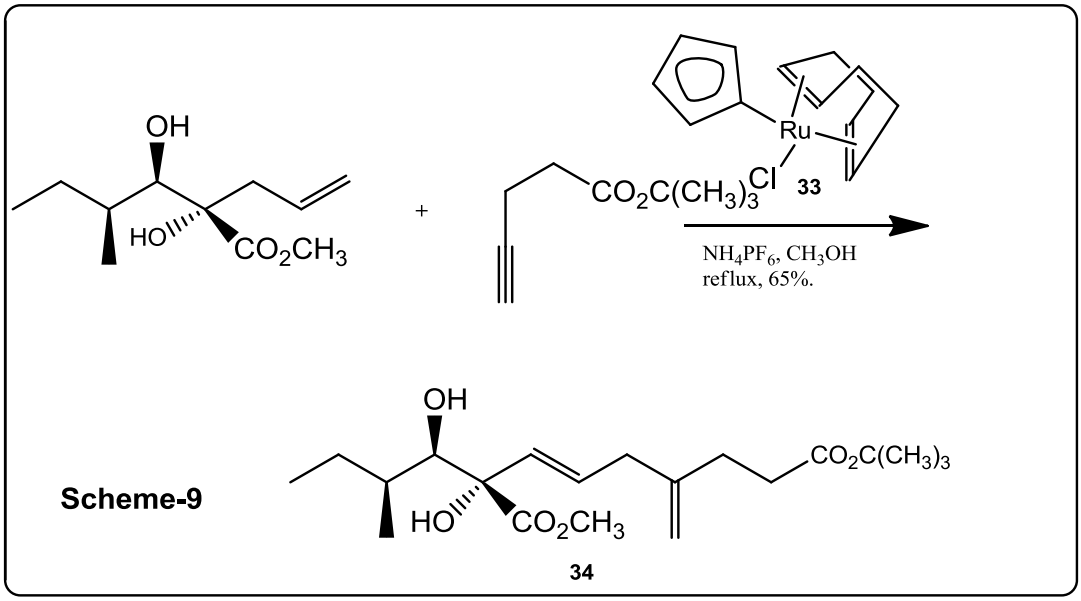


Scheme - 7



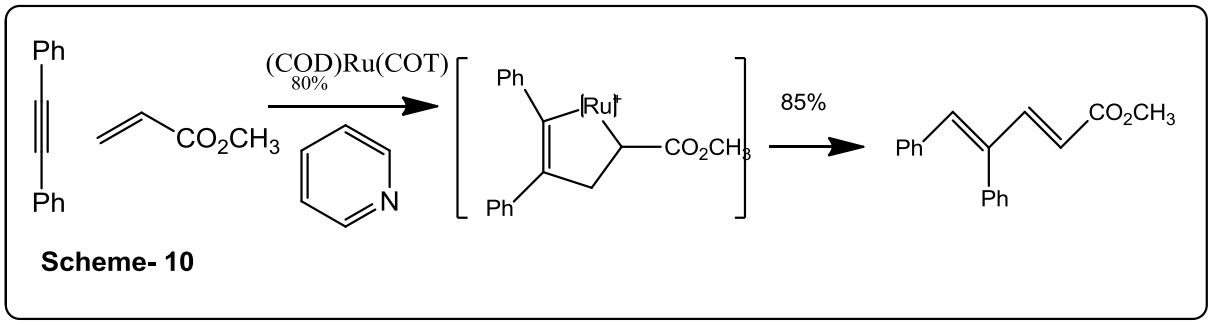
Scheme -8

There has been regular efforts on carbon- carbon bond formation using Ruthenium catalysis from many prominent groups throughout the world. Trost Group from Stanford University, USA has made pioneering contributions on this emerging field. For e.g. the group has used ruthenium catalysis to accomplish alkene-alkyne coupling, using catalyst **(33)** to generate **(34)** which is a key step towards the synthesis of alternaric acid. **(Scheme-9)**



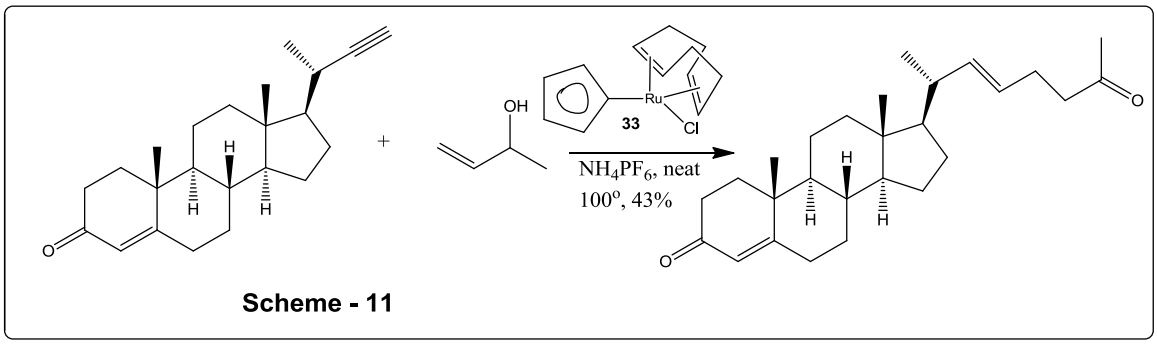
Scheme-9

Wantabe *etal*. has proposed a similar ene-yne addition using (COD)Ru(COT) catalyst where a 1,4-diene is formed. **(Scheme – 10)**



Scheme- 10

Dixneuf *etal*. used the same catalyst (33) to synthesise γ,δ- unsaturated ketones with steroid skeleton.



Scheme - 11

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