Title: RUTHENIUM-CATALYSED ATOM-ECONOMIC TRANSFORMATIONS

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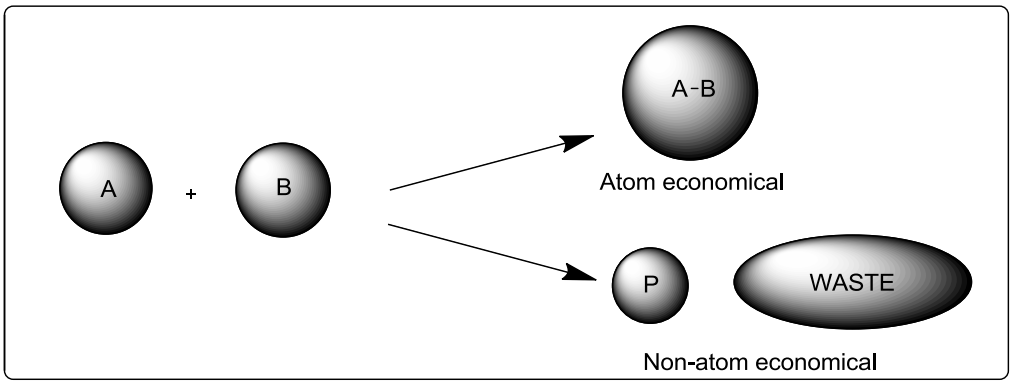
Introduction

At the heart of any chemical synthesis of a natural product or designed small molecule is the need to orchestrate a series of chemical reactions to prepare and functionalize a carbon framework. The advent of transition-metal catalysis has provided chemists with a broad range of new tools to forge C−C and C−X bonds and has resulted in a paradigm shift in synthetic strategy planning. The ruthenium catalysed C−C coupling reaction of propargyl alcohol and Michael acceptor has been demonstrated an enabling methodology for synthesis o α,β-unsaturated ketones as a single geometrical isomers of high yield in an atom-economical fashion. The synthesized α,β-unsaturated ketones are the precursor of poly-substituted piperidones and hexahydroisoquilininones which are the central backbone of many biologically active natural products and pharmaceutical drugs.

The chemistry of ruthenium is very interesting due to its ability to assume a wide range of oxidation states (from -2 to +8) and coordination geometries provides unique opportunities for catalysis. As such, a wide range of mechanistically very different processes are catalyzed by ruthenium. These include reactions initiated by metallocycle formation, vinylidene formation, C-H activation, and activation of carbon-carbon multiple bonds by coordination. These catalysts are generally the most versatile due to the facile redox chemistry between those oxidation states and therefore have the greatest ability to react in catalytic cycles.

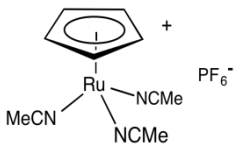
The coupling reactions of ruthenium catalyst are metathesis and non-metathesis. The metathesis coupling is an organic reaction that entails the redistribution of fragments of alkenes (olefins) by the scission and regeneration of carbon-carbon double bonds with loss of one olefin molecules which is performed by Grubbs catalyst. The non-metathesis couplings is the reaction where two alkene, alkyne or allene can couple atom economically together to form a new species where no loss of molecules which is performed by tris(acetonitrile)cyclopentadienyl ruthenium(ii) hexafluorophosphate catalyst.

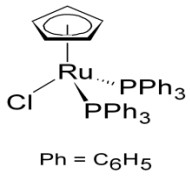
The main importance of non-metathesis couplings are atom-econmical transformation. It is the aim to convert in readily available starting materials into the target molecules in relatively few synthetic steps with keeping the generation of side product and waste on smallest level possible.



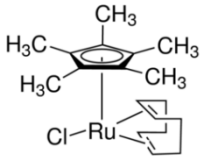
If the maximum atoms of reactant appear in the product a reaction can be called atom economic which is introduced by Barry M. Trost and he also published a review on " Atom Economy-A Challenge for

Organic Synthesis :Homogeneous Catalysis Leads the Way "[1]. Classical examples are Diels-Alder reactions, aldol reactions and rearrangements. The activation of organic molecules with catalytic amounts of transition metal complexes is an attractive method for developing process with high atom economy.Some important catalyst, responsible for atom economic non-metathesis couplings are:

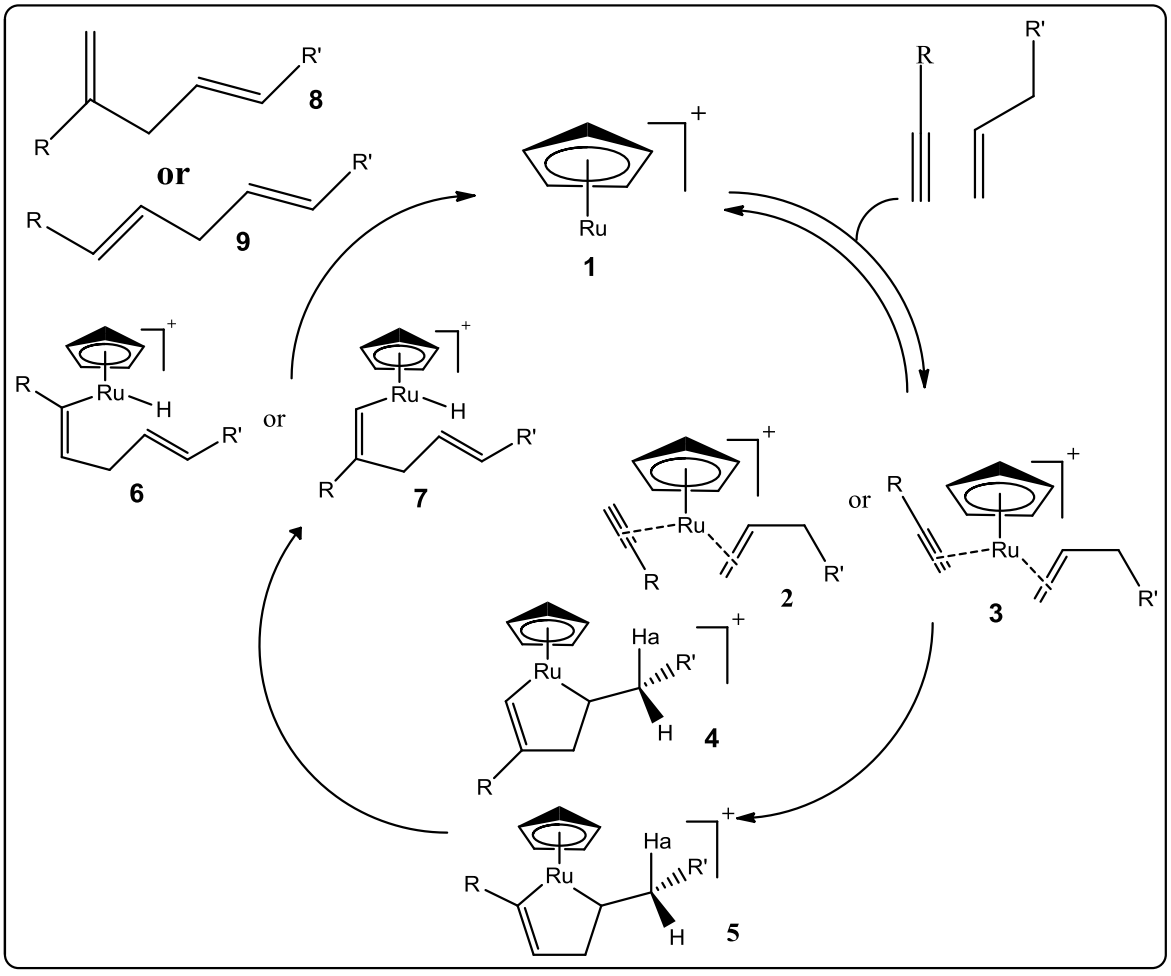




Ph = C_6H_5



The catalytic cycle of non-metathesis couplings are:

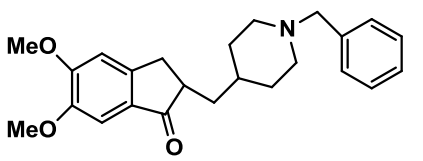


Besides the C−C bond formation, the C−X bond formation by metal catalysed coupling reaction in an atom economical fashion has also great importance due to the moieties like pyrrole, furan, thiopnene, pyridine,

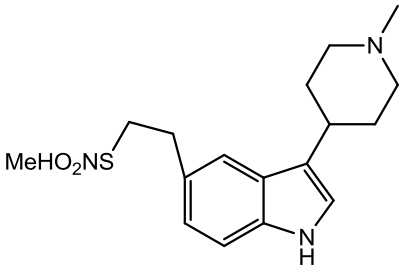
indole, benzofuran etc which are the central key core of many important biologically active natural product, can be synthesized in one step which is not so easy by conventional pathways.The high yielding and essentially pure 5-memberd aromatic heterocycles, Di and Tri-substituted pyrrole are efficiently synthesized from 1,5-Bocamino alcohol by using transition metal catalyst.

Ruthenium Catalysed Non-metathesis Couplings to Generate Polysubstituted Piperidones and Attempt Towards Synthesis of Polysubstituted Hexahyroisoquilinones

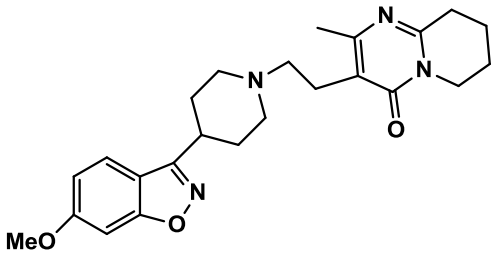
Our work started with the idea of development of the polysubstituted 1,4-piperidone system in an atom-economical fashion mainly with Ruthenium catalysis. The functionalized piperidone can further be easily reduced to the desired piperidine system. The functionalized piperidine rings are the central backbone of many alkaloidnatural products and thus continues to be a common moiety in pharmaceuticalresearch. Piperidones as a whole do not comprise more of these natural products butthey act as advanced intermediates for piperidine synthesis. There are many recent reviews which update the progress of stereoselective and asymmetric syntheses of substituted piperidines[2]. There are many latest pharmaceutically important products which contain a pyridine as a central core[3].



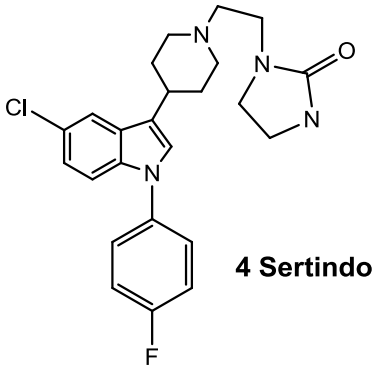
1 Donepezil (An Acetyl Cholineesterase inhibitor)



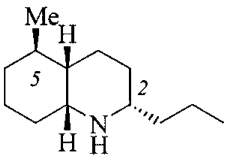
2 Naratriptan



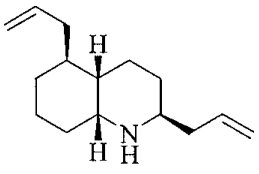
3 Risperidone (Antagonist against Schizophrenia)



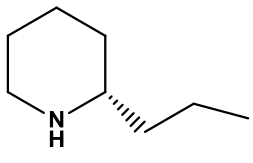
4 Sertindole



5 Pumiliotoxin C,



6 *cis*-**219A**

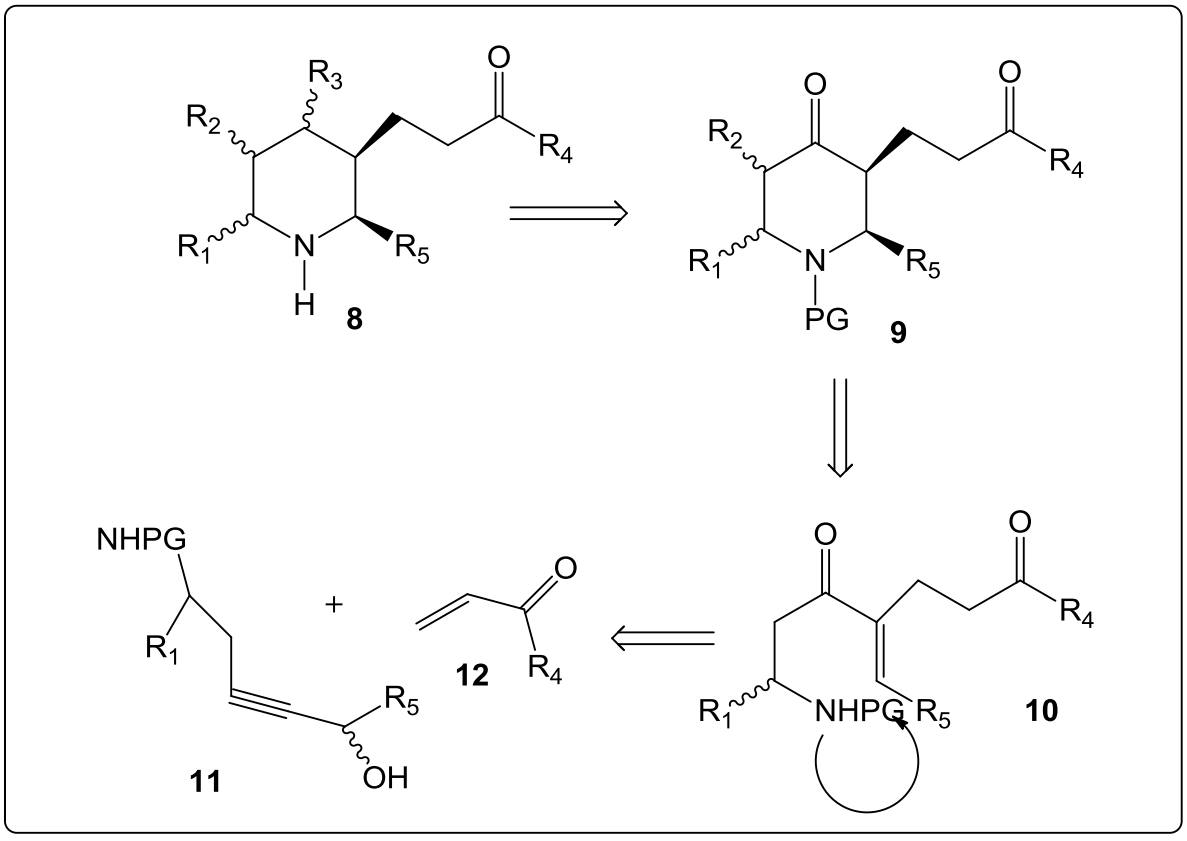


7 Conine

Aricept 1(Donepezil), an acetylcholineesterase inhibitor, is currently being prescribed for Alzeimer,s syndrome. Naramig (naratriptan) 2, an antagonist of 5-HT1D and 5-HT1B has shown promise in the treatment of migraine headaches. Risperdal(Risperidone) 3, and Serdolect 4, both non-selective 5-HT/D2 antagonists are currently being utilized in thetreatment of schizophrenia. Apart from these four, there is a huge variety of piperidine natural products with an extensive range of biological activities.

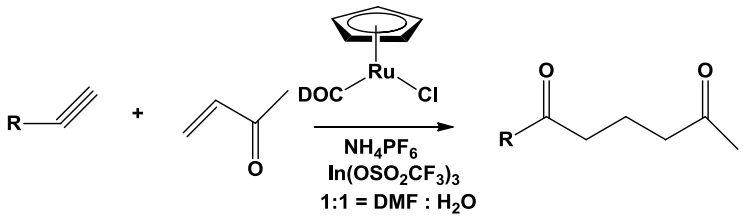
Retrosynthetic View

Retrosynthetically we envisaged that a well functionalized piperidine (**8**) can be achieved from reduction of a 1,4-piperidones (**9**) which can further be achieved from an intramolecular Aza-Michael type addition to a α,β- unsaturated ketone by the N-protected amine (**10**). The N-protected amine (**10**) can be synthesized from the coupling reaction of a propargyl alcohol (11) and a Michael acceptor like Methyl-vinyl ketone (12).

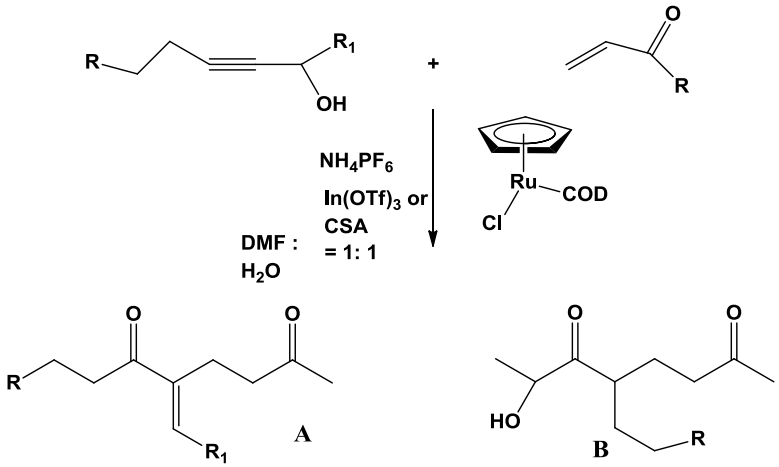


Literature Survey

From literature survey, we have seen that there are few reports of coupling of propargyl alcohols and Michael acceptor like methyl-vinyl ketones[4]. Initially, the First Generation of the catalyst CpRu(COD)Cl was used. Later a four component coupling was

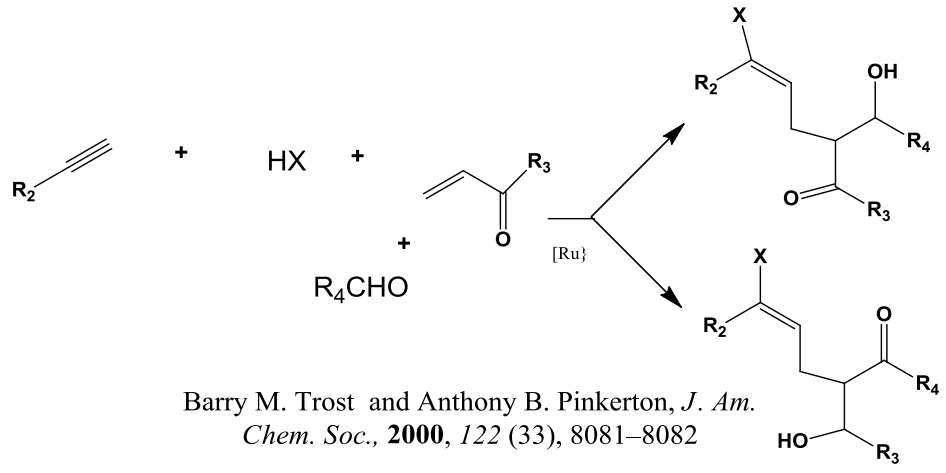


Barry M. Trost , Moshe Portnoy , and Hideki Kurihara, *J. Am. Chem, Soc.,* **1997**, *119*, 836-837



Entry	R	R_1	Isolated Yield A : B	Ratio A : B
1.	H	C_2H_5	55 : 19	3 : 1
2.	n- C_4H_9	C_3H_7	48 : 8	6 : 1
3.	OH	H	80 : < 1	> 80 : 1

Barry M. Trost, Lars Krause, and Moshe Portnoy, *J. Am. Chem. Soc.* **1997**, *119*, 11319-11320



Barry M. Trost and Anthony B. Pinkerton, *J. Am. Chem. Soc.,* **2000**, *122* (33), 8081–8082

reported by using second generation $CpRu(CH_3CN)_3^+PF_6^-$. From literature survey we conclude that the

best catalyst for this couplings would be $CpRu(CH_3CN)_3^+PF_6^-$ [5].

Having all these in mind, it was decided to start with the Boc-imine **(15)** as the starting substrate. The Boc-imine **(15)** was prepared by a convenient two step procedure from benzaldehyde, sodium benzene sulfinate and tert-butyl carbamate[6].The next step was to generate the propargyl zinc solution in situ and add it to the BOC-imine.