SYNOPSIS

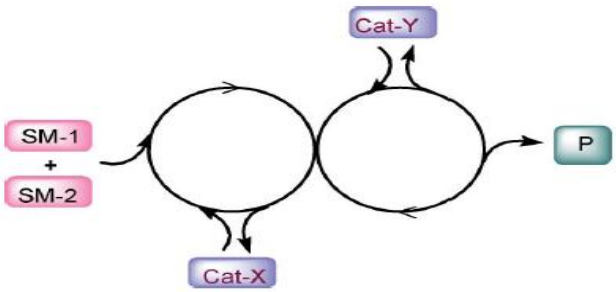
Thesis Title: Cooperative multicatalytic Prins cyclization for the synthesis of octahydrospiro-*β*-carboline, tetrahydropyranoquinoline and spiro-tetrahydropyrano morpholine derivatives

The thesis mainly deals with the studies on Cooperative multicatalytic Prins cyclization reactions catalyzed by gold and Lewis acid catalysts. The main emphasis is on the synthesis of oxygen and nitrogen containing heterocyclic compounds. The work embodied has been divided into four chapters.

CHAPTER I: This chapter divided into section A & B

SECTION A: *This section deals with the overview of concept namely Cooperative multicatalysis.*

The development of multicatalytic cascade reactions for "one pot" synthesis of complex multi-ring molecular architectures is fuelled by its synthetic efficiency, atom economy, and yield loss associated with isolation and purification. This section demonstrates a brief overview of the progress, which has been made in the field of cooperative multicatalytic reactions over the past few years. Many examples of related concept with their applications towards the synthesis of biologically active compounds have been discussed.



Cooperative Catalysis

SECTION B: *Introduction to Prins reaction, mechanism, its variations and its application in total synthesis of Natural Products*

The development of catalytic cascade reactions for "one pot" synthesis of complex heterocyclic architectures is fuelled by its synthetic efficiency, atom economy and high selectivity. This chapter demonstrates a brief overview of the progress, which has been made in the field of Prins reaction over the past few years. Many examples of

their applications towards the synthesis of biologically attractive compounds have been discussed. Keeping in mind the potential of the above two concepts and shortcomings, we endeavored to initiate work in this direction which is described in chapter **2-4**.

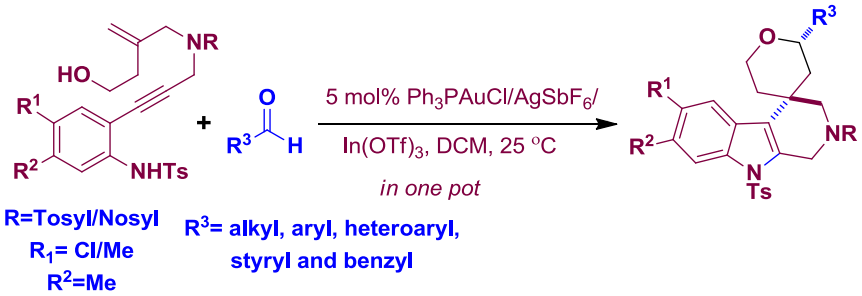
CHAPTER II

Domino strategy for the stereoselective construction of octahydrospiro-*β*-carbolines.

This chapter deals with the designing Cooperative Multicatalytic System for the One-Pot Synthesis of Octahydrospiro-β-carbolines.

Tetrahydro-*β*-carbolines (THBC) are often found in naturally occurring indole alkaloids and are considered as privileged scaffolds in medicinal chemistry. Owing to their inherent biological properties, several efforts have been made to generate the diversified THBCs through a Pictet−Spengler reaction of tryptophan or tryptamine with aliphatic or aromatic aldehydes under acidic conditions. In particular, spiro-THBCs are important pharmacopores and found in several pharmaceuticals. For example, spiro-indolinone, i.e., NITD609, is a potent antimalarial lead in nanomolar scale and kills the blood strain of Plasmodium falciparum. However, only a few methods have been developed for the synthesis of spiro-THBCs. Therefore, the development of a one-pot strategy for the synthesis of spiro-THBCs is enviable to generate structural complexity and diversity for drug discovery. Recently, domino cyclization of 2-alkynylanilines has become a powerful synthetic route for the synthesis of indoles and quinolines. A large number of reagents are reported for the conversion of 2-alkynylanilines into 2-substituted indoles. Among them Au complexes are well explored for the above transformation due

Methodology developed:



Scheme 1: One-pot Synthesis of octahydro spiro-*β*-carbolines

to their high alkynophilicity and Lewis acidity to promote further C−C or C−X bond formation. Inspired by recent advancement in multicatalytic systems, we herein disclose a novel cascade strategy for the one-pot synthesis of octahydrospiro[pyran-4,4′-pyrido[3,4-b]indole] derivatives from 3-((3-(2-aminophenyl)prop-2-ynylamino) methyl)but-3-en-1-ol and aldehydes through a multicatalytic cascade cyclization.

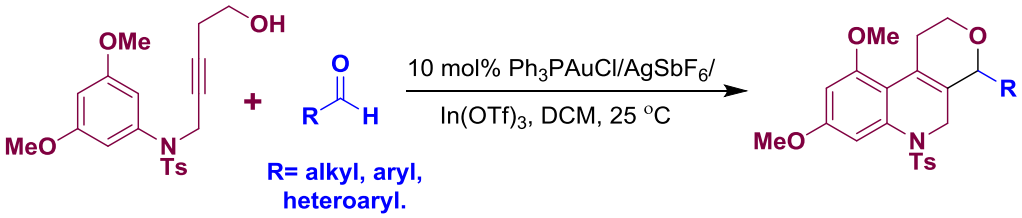
CHAPTER III

Synthesis of tetrahydropyranoquinoline derivatives through a Prins cascade cyclization.

This chapter deals with the construction of tetrahydropyranoquinolines derivatives via Prins/Friedel-Craft cascade strategy.

The Pyranoquinoline core is found in many alkaloids such as flindersine, oricine, veprisine, and (+)-orixalone D. These alkaloids and their derivatives possess a wide range of biological activities such as psychotropic, antiallergenic, anti-inflammatory, and estrogenic activities. Thus, pyrano quinolines and their synthetic analogues are of great interest because of their potent biological activities. Generally, the pyranoquinolines are prepared by a well-known Povarov reaction that involves the reaction of aniline with benzaldehyde and alkene in the presence of an acid catalyst. In this chapter we have described a cascade reaction of N-(3,5-dimethoxyphenyl)-N-(5-hydroxypent-2-yn-1-yl)-4-methylbenzenesulfonamide with various aldehydes in the presence of Ph_3PAuCl + $AgSbF_6$ + $In(OTf)_3$ in dichloromethane at 25 °C which affords a novel class of tetrahydropyrano quinolines in good yields.

Methodology developed:



Scheme 2: Synthesis of tetrahydropyrano quinolines

As a model reaction, we first attempted the condensation of N-(3,5-dimethoxy phenyl)-N-(5-hydroxypent-2-yn-1-yl)-4-methylbenzenesulfonamide with 4-bromo benzaldehyde using with several Lewis acids such as $InCl_3$, $FeCl_3$, $Sc(OTf)_3$, $In(OTf)_3$, $BF_3.OEt_2$, and TMSOTf in dichloromethane. However, no desired cyclization was observed. After screening several catalysts, the $Ph_3PAuCl/AgSbF_6/In(OTf)_3$ catalyst system was found to be the best to afford the desired product in 80% yield, which was confirmed by the H^1 & C^{13} NMR spectrum. Various aldehydes having diverse electronic character were tested and found to tolerate reaction conditions very well.

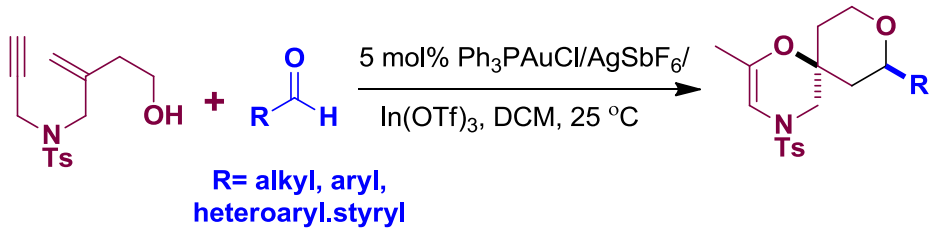
CHAPTER IV

This chapter describes the construction of spirocyclic scaffolds using Prins cascade cyclization.

This chapter deals with the designing and synthesis of spiro-tetrahydropyrano morpholine derivatives via Prins cyclization strategy.

Spiroketal derivatives possessing a nitrogen atom have been evaluated as tachykinin antagonists. In particular, spiro-morpholine derivatives have been found to exhibit high affinity and excellent central nervous system penetration. They are known to display a broad spectrum of biological activities such as antiproliferative, anti-HIV, and NK1 receptor antagonist behavior. In this section, a novel Prins cascade process for the synthesis of 1,9-dioxa-4-azaspiro[5.5]undec-2-ene derivatives by the coupling of aldehydes with N-(4-hydroxy-2-methylenebutyl)-4-methyl-N-(prop-2-yn-1-yl) benzene sulfonamide has been disclosed.

Methodology developed:



Scheme 3: synthesis of spiro-tetrahydropyranomorpholines