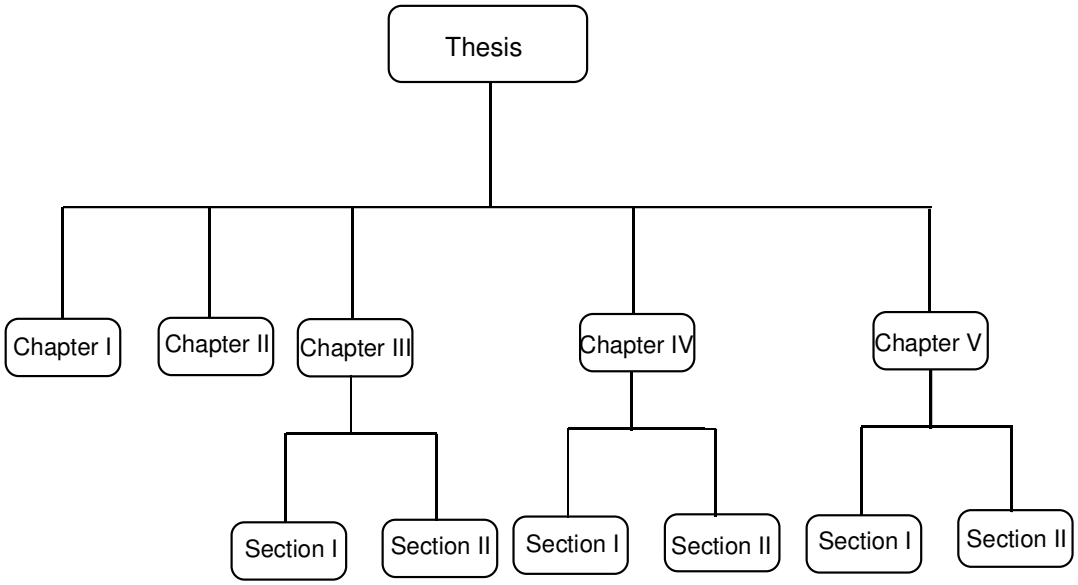
CORE
Metadata, citation and similar papers at core.ac.uk
Provided by Open Access Repository of Indian Theses

Nanocrystalline Magenesium oxide / Pyrrolidine Derivatives for Selective and Enantioselective Organotransformations

The thesis, which begins with an introduction (Chapter 1), followed by 4 chapters is outlined here.

Organization of the thesis



The thesis mainly deals with the applications of nanocrystalline metal oxide and organocatalysts for various organic transformations. The first chapter mainly deals with the importance and applications of heterogeneous catalysis, importance of nanocrystalline materials for site selective catalysis. The need and development of cleaner and greener alternative technologies using truly heterogeneous catalytic system in the synthesis of pharmaceuticals and fine chemicals is also described. Chapter II mainly deals with the development of nanocrystalline magnesium oxide for direct asymmetric aldol reaction to afford the chiral β-hydroxy carbonyl compounds. Chapter III describes the synthesis of β-

hydroxy-α-diazo carbonyl compounds and Mukaiyama aldol adducts by using nanocrystalline magnesium oxide catalyst. Chapter IV describes the synthesis of Baylis-Hillman adducts of cyclic enones and aldehydes and also β-nitroamine derivatives by using nanocrystalline magnesium oxide. Chapter V mainly deals with the use of organocatalysts in green reaction media such as ionic liquids and water for the synthesis of β-hydroxy-α-diazo carbonyl compounds and chiral aldol adducts.

CHAPTER – I

INTRODUCTION

This chapter describes various catalyst/ process options available for an industrial chemist to effect different organic transformations. It includes a brief introduction of homogeneous, heterogeneous, heterogenized homogeneous catalytic systems, nanocrystalline materials and its applications in catalysis and basic concept commonly encountered in catalysis such as selectivity, turnover number, atom economy etc. The importance of selective organic transformations and the need for the design and development of nanocrystalline materials.

This chapter also describes the importance of organocatalysts as catalysts for organic synthesis. The importance of ionic liquids and aqueous media for the selective and enantioselective organic transformations is also described.

CHAPTER - II

Direct asymmetric aldol reaction catalyzed by nanocrystalline magnesium oxide.

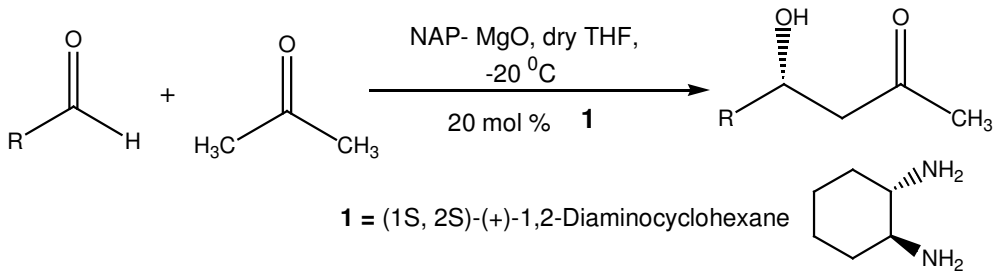
This chapter describes the use of nanocrystalline magnesium oxide for the direct asymmetric aldol reaction of various aromatic aldehydes and acetone to afford chiral β-hydroxy carbonyl compounds. The direct aldol reaction is a very important carbon-carbon

bond formation reaction in organic synthesis with numerous applications in industry and in laboratory and is classically catalyzed by both Lewis acids and bases. The aldol products, β-hydroxy carbonyl compounds can be readily converted into 1,3-syn and anti-diols and amino alcohols, which are the building blocks in many natural products such as antibiotics, pheromones and in many biologically active compounds. The aldol products have been successfully converted to the key synthetic intermediates of epithilone A and bryostatin 7. The main limitations in the current processes are the use of stoichiometric amount of base to substrate, longer reaction times, lower yields, and generate large quantities of salts by neutralizing bases or vice-versa, which renders the process incompatible to the environment and uneconomical.

Transition metal chiral complexes, single site catalysts with a defined shape and stereochemistry induce in general higher enantioselectivity in asymmetric synthesis, since they permit unidirectional introduction of a reacting species on to the prochiral substrate in a three dimensional space to generate an asymmetric centre. Conversely, heterogeneous catalysts are not as effective as transition metal chiral complexes due to their multi active sites resulted from assorted crystal structures with different shapes and sizes and also their steric restrictions. Hence, creation of desired stereochemistry with defined shape and size in heterogeneous catalysts to build the asymmetric centre is a challenging problem. Nanomaterials have become potential candidates for wide and divergent applications that include biomedicals, pharmaceuticals and catalysis. Nanomaterials with their three dimensional structure and defined size and shape are considered to be suitable candidates for proper alignment with prochiral substrates enables unidirectional introduction of reacting species to induce asymmetric centre.

In this regard we described the use of a truly nano heterogeneous catalyst, NAP-MgO for the direct asymmetric aldol reaction of various aldehydes and acetone to afford

chiral β-hydroxy carbonyl compounds with good yields and moderate to good enantioselectivities (ee's) (Scheme 1).



Scheme 1.

.

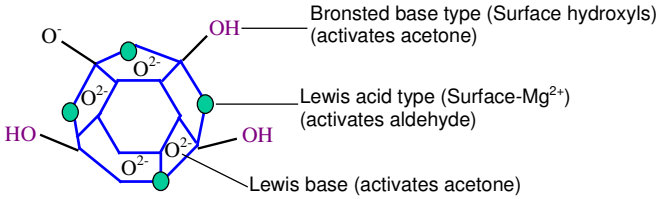


Fig. 1. Structure of NAP-MgO

The nanocrystalline magnesium oxide (aerogel prepared) NAP-MgO was found to be superior to the conventionally prepared magnesium oxide (CP-MgO) and commercial magnesium oxide (CM-MgO) in terms of activity and enantioselectivity as applicable in these reactions. This is because of NAP-MgO having high surface concentrations of edge/corner and various exposed crystal planes (such as 002, 001 and 111), leads to inherently high surface reactivity per unit area. An elegant strategy for heterogenization of homogeneous catalysts is presented here to evolve single site catalyst for direct asymmetric aldol reaction by a successful transfer of molecular chemistry to surface metal-organic chemistry with the retention of activity, selectivity/enantioselectivity.

High lights of the present catalytic system

This heterogeneous nanocrystalline catalyst will be a practical alternative to soluble bases for the direct aldol reactions in view of the following advantages, a) truly heterogeneous b) high catalytic activity under very mild reaction conditions, c) easy

separation of the catalyst by simple centrifugation d) the catalyst is easy to handle and reusable for several cycles without loss of activity, and enantioselectivity and e) The present method is simple and clean over the existing procedures.

CHAPTER- III

This chapter is divided into two sections.

Section I: Synthesis of α-diazo-β-hydroxy esters using nanocrystalline magnesium oxide

The synthesis of diazo compounds is of great interest as the α-diazo carbonyl compounds bearing a β-hydroxyl group can undergo diverse synthetically useful transformations. This transformation is very useful as we can introduce a diazo group as well as a hydroxy group in a single step. Moreover, the carbene species generated from α-diazo carbonyl compounds are widely used in molecular insertion reactions to form new C-C and/ or C-heteroatom bonds. α-diazo-β-hydroxy carbonyl compounds are generally prepared by the azido transfer reaction of carbonyl compounds. These diazo compounds are generally synthesized by the condensation of aldehyde and ethyl diazoacetate in presence of a base under homogeneous conditions.

The main limitations in the current processes are the use of stoichiometric amount of base to substrate, longer reaction times and higher temperatures needed to carry out the reaction, which renders the process incompatible to the environment and uneconomical. In this regard, we chose nanocrystalline form of MgO, since it is having basic sites in high density.

Herein the aldol-type reaction of various aldehydes and ethyl diazoacetate to afford α-diazo-β-hydroxy esters in excellent yields with high selectivity under mild conditions using nanocrystalline magnesium oxide is described (Scheme 2).

Scheme 2.

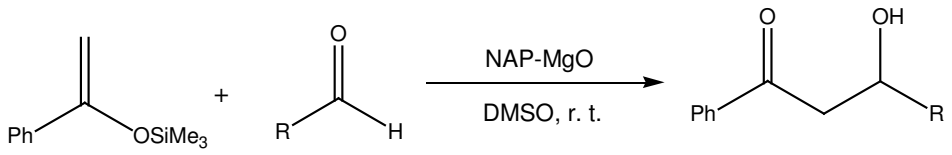
Section II: Mukaiyama aldol reaction of silyl enol ethers with aldehydes by using nanocrystalline magnesium Oxide

The aldol reaction is considered as one of the most important carbon-carbon bond forming reactions in organic synthesis. In particular aldol reaction of silyl enol ethers with aldehydes (the Mukaiyama aldol reaction) has emerged as an important and versatile synthetic tool in organic and biochemical domains. This reaction provides a synthetic route for β-hydroxy carbonyl compounds via carbon-carbon bond formation. The Mukaiyama aldol reaction can be catalyzed either by Lewis acids via activation of the electrophiles (i.e., carbonyl compounds) or by Lewis bases via activation of the nucleophiles (i.e., enoxysilanes).

Despite the widespread use of the Lewis acid catalysts for the Mukaiyama aldol reaction, various Lewis base catalysts have also been developed. Although high selectivity for the desired products was achieved, there were many drawbacks under homogeneous conditions including catalyst recovery and waste disposal problems. Industry favors catalytic processes induced by heterogeneous catalysts over homogeneous catalysts in view of the ease of handling, simple work-up and regenerability.

Herein the Mukaiyama aldol reaction of various aldehydes and silyl enol ethers to afford the corresponding β-hydroxy carbonyl compounds in good to excellent yields with

high selectivity under mild conditions using nanocrystalline magnesium oxide is described (Scheme 3).



Scheme 3.

Advantages. Compatible Bronsted basic hydroxyl sites present in the nanocrystalline magnesium oxide give rise to β-hydroxy carbonyl compounds in excellent yields in shorter times, which is superior than the methodologies described earlier. a) high catalytic activity under mild liquid phase conditions, b) easy separation of the catalyst by simple centrifugation, c) excellent yields of Mukaiyama aldol products at faster rates of reaction, d) use of non-toxic and inexpensive materials, e) recycling of the catalyst, and f) zero emission of pollutants. The present catalytic system is thus a potential alternative to homogeneous catalytic systems.

CHAPTER - IV

This chapter is divided into two sections.

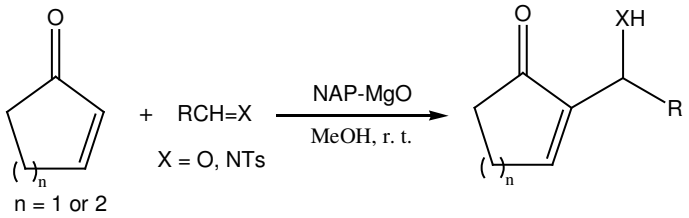
Section I: Baylis-Hillman reaction of cyclic enones with arenecarbaldehydes and *N*-arylidene-4-methylbenzenesulfonamides by using NAP-MgO.

Carbon-carbon bond formation is one of the most fundamental reactions in organic synthesis. The Baylis-Hillman reaction, which involves the coupling of activated alkenes with carbon electrophiles in the presence of Lewis base catalysts (most commonly tertiary amines, particularly 1,4-diazabicylco [2.2.2] octane (DABCO)), is among the most useful

C-C bond-forming tools to afford the structural building blocks in biological and medicinal chemistry.

Although a large variety of activated alkenes were successfully employed in the Baylis-Hillman reaction, still this reaction was inefficient for cyclic enones. Under the normal traditional Baylis-Hillman reaction conditions, DABCO was found to inefficient for the reactions of cyclic enones and arenecarbaldehydes. In addition, 1, 8-Diazabicyclo [5.4.0] undec-7-ene (DBU) and aqueous trimethylamine lead to self-dimerisation of the cyclic enones. Several methods were developed for the Baylis-Hillman reaction of aldehydes/*N*-benzylidene-4-methylbenzenesulfonamides with cyclohex-2-en-1-one or cyclopent-2-en-1-one in the presence of various Lewis acids and Lewis bases to afford the Baylis-Hillman adducts with good yields.

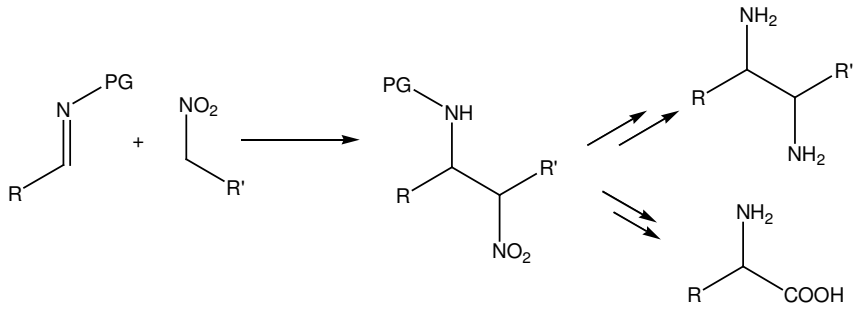
Nanocrystalline metal oxides find excellent applications as active adsorbents for gases and destruction of hazardous chemicals and as catalysts for various organic transformations. In this regard the use of nanocrystalline magnesium oxide (NAP-MgO) for the Baylis-Hillman reaction of cyclic enones with arenecarbaldehydes and *N*-benzylidine-4-methylbenzenesulfonamides to afford the Baylis-Hillman adducts in moderate to good yields with high selectivity under mild conditions is described. (Scheme 4).



Scheme 4.

Section II: Synthesis of β-nitroamine derivatives using nanocrystalline magnesium oxide.

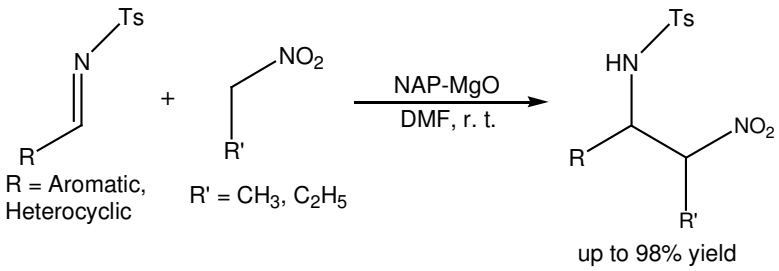
The formation of carbon-carbon bonds is one of the most fundamental reactions in organic synthesis. The Henry or nitroaldol reaction is a useful carbon-carbon bond forming process. In particular, the direct aza-Henry (nitro-Mannich) reaction has become a viable transformation for the synthesis of nitrogen containing compounds. The aza-Henry reaction provides a valuable method for the synthesis of β-nitroamines through the nucleophilic addition of nitroalkanes to imines. The β-nitroamines can be further converted into useful building blocks such as 1,2-diamines and α-aminoacids by reduction and Nef reaction of the nitro moiety (Scheme 5).



Scheme 5.

A number of electron-deficient imines, carrying imine-activating groups such as *N*-phosphinoyl imine, α-iminoester and N-Boc imines were studied for the aza-Henry reaction. However, the more stable *N*-tosyl imine was less explored for the aza-Henry reaction. The toluene-sulfonyl activating group of imine can be removed easily by treatment with Mg/MeOH, treatment with phenol in refluxing HBr/HOAc solution with addition of H_2O, or treatment with SmI_2 in THF at room temperature.

Herein the aza-Henry reaction of various *N*-sulfonyl imines and nitroalkanes to afford the corresponding β-nitroamines in excellent yields with high selectivity under mild conditions using nanocrystalline magnesium oxide (NAP-MgO) is described (Scheme 6).



Scheme 6.

CHAPTER - V

This chapter is divided into two sections.

Section I: Pyrrolidine catalyzed condensation of ethyl diazoacetate to aldehydes in water

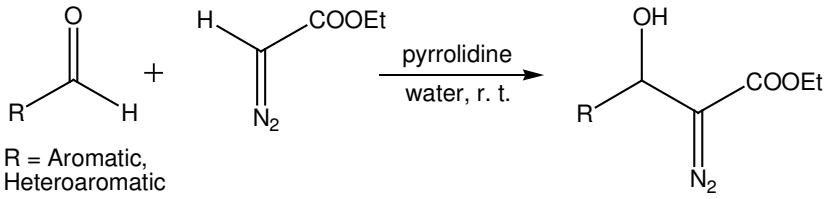
Catalytic transformations involving small organic molecules, known as 'organocatalysis', has attracted much interest in recent years. A small organic molecule, especially proline is used for a variety of organic transformation such as aldol, Michael and Mannich reactions. Though a number of these reactions have been performed in organic solvents, use of aqueous media is much more attractive from environmental considerations. Moreover, these molecules may act as enzyme mimics in water, which is the natural environment of biological reactions.

The aldol reaction is considered as one of the most important carbon-carbon bond forming reactions in organic synthesis. The carbon-carbon bond formation is a challenging task in modern organic synthesis as the direct aldol reaction is highly atom efficient. The corresponding catalytic aldol reaction has been extensively studied over the past decades, and number of catalytic systems have been developed. New and powerful

variants of these classical reactions have been developed in recent years. The direct catalytic aldol reaction has been studied only recently for the synthesis of α-diazo compounds, which are of great interest. α-Diazo carbonyl compounds are generally prepared by diazo transfer reactions of carbonyl compounds. The recent developments in Lewis acid mediated aldol-type reaction and base catalyzed intramolecular and intermolecular aldol type reactions have been shown to take place at the diazo carbon of some diazomethyl ketones. Under normal base catalyzed reactions the aldol-type reaction proceeds without destruction of the '$–CON_2$' moiety.

Diazo carbonyl compounds have attracted great attention, as these compounds can undergo diverse synthetic useful transformations. Ethyl diazoacetate reacts with a variety of aldehydes in the presence of a Lewis acid catalyst to give β-ketoesters, α,β-epoxy esters (glycidic esters), and cyclopropinated compounds with the loss of diazo group.

Pyrrolidine and pyrrolidine-derived organocatalysts were shown to be much more efficient catalysts for C-C bond forming reactions. Herein the direct aldol type reaction of various aldehydes and ethyl diazoacetate to afford the β-hydroxy-α-diazo carbonyl compounds in good yields with high selectivity under mild conditions using pyrrolidine as a catalyst in aqueous media is described (Scheme 7).



Scheme 7.

Section II: L-Proline catalyzed direct asymmetric aldol reaction of hetero-aromatic aldehydes and acetone: Higher selectivity in room temperature Ionic liquid bmim [BF_4]

Asymmetric C-C bond formation is of great importance in pharmaceutical, agrochemical and fine chemical industries. Interest in asymmetric synthesis continues to increase and this has heightened the need for the design of highly selective asymmetric catalysts. The aldol reaction is considered to be one of the most important carbon-carbon bond forming reactions in both the biochemical and chemical domains. The aldol reaction is ubiquitous in synthetic organic chemistry to generate the elegant intermediates of anti-hypertensive drugs and calcium antagonists.

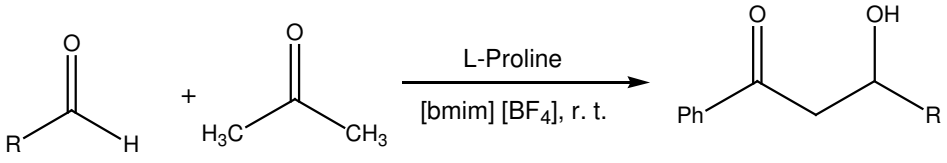
Small organic molecules in place of enzymes or metal complexes represent a remarkable synthetic alternative to many established asymmetric transformations. The simplest catalyst system reported for the direct asymmetric aldol reaction involves the use of amino acid catalysts, which function as Class I aldolase mimics. The first example of asymmetric catalysis using small organic molecule was the Hajos–Parrish–Eder–Sauer–Wiechert reaction, an intramolecular aldol reaction catalyzed by proline. About 30 years later, List et al. followed by other research groups, discovered proline-catalyzed enantioselective intermolecular aldol reactions.

However, the reactivity and selectivity of some of these proline catalyzed aldol reactions have serious limitations because of the structurally modifying proline. Furthermore, a substoichiometric amount of proline is often necessary to achieve reasonable yields in the direct aldol reaction of aldehydes with acetone. Also, proline is known to react with electron-deficient aromatic aldehydes to form imminium salts, which undergo decarboxylation, even at room temperature. Such degradation may induce the

significant retardation of the proline-catalyzed aldol reactions. In particular heteroaromatic aldehydes were not prone to endure the aldol reaction in presence of proline. Since, proline reacts with the heteroaromatic aldehydes to form imminium salts, which undergo undesirable degradation through decarboxylation even at room temperature. In order to polarize the imminium salt formed, the reaction media should be highly polar in nature. The expense of enantioselectivity renders the use of aqueous media for the direct asymmetric aldol reaction using proline as organocatalyst. Room temperature ionic liquids were shown to be a good alternative to the aqueous media in order to accomplish the same enantioselectivity.

Ionic liquids have been widely used as environmentally benign solvents to replace common organic media. Moreover, they are reusable, allow for simple isolation of products and enable the easy recovery of catalysts. More interesting is the enhancement of reaction efficiency by using ionic liquids as solvents. Aldol reactions in the presence of L-proline in ionic liquids have been documented, but reduced enantioselectivity was observed in most of cases.

The direct asymmetric aldol reaction of different heterocyclic aldehydes with acetone using L-proline in ionic liquids at room temperature is described (Scheme 8).



Scheme 8.

The direct asymmetric aldol reactions of heteroaromatic aldehydes with acetone in imidazolium-based ionic liquids are investigated. Under the optimal conditions, higher yields and good enantioselectivities are obtained. L-proline in ionic liquid can be reused for three cylces with constant yields and enantioselectivities. The asymmetric reaction

using a chiral catalyst in ionic liquid greatly enhances the synthetic value of ionic liquid as green reaction media.

Significant Achievements

- Development of truly asymmetric heterogeneous catalyst for direct asymmetric aldol reaction with good yields and moderate enantioselectivity.
- Evaluation of single site catalyst for the synthesis of β-hydroxy-α-diazo carbonyl compounds and β-hydroxy carbonyl compounds using direct aldol type reaction and Mukaiyama aldol reaction.
- Evolution of nanocrystalline MgO as an efficient heterogeneous catalyst for the Baylis-Hillman reaction of arene carbaldehydes and *N*- sulfonyl imines with cyclic enones.
- Evaluation of nanocrystalline MgO as a highly efficient heterogeneous catalyst for the direct aza-Henry reaction of *N*- sulfonyl imines and nitromethane.
- Evaluation of organocatalysts L-proline and pyrrolidine as efficient catalysts for the direct asymmetric aldol reaction and direct aldol type reaction in ionic liquid and water as green reaction media.