Ph.D. Thesis Summary

Synthesis and Characterization of Catalytic Materials and their application in Organic Transformations

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IN

CHEMISTRY

सत्यं शिवं सुन्दरम्

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Table of Contents of the Thesis

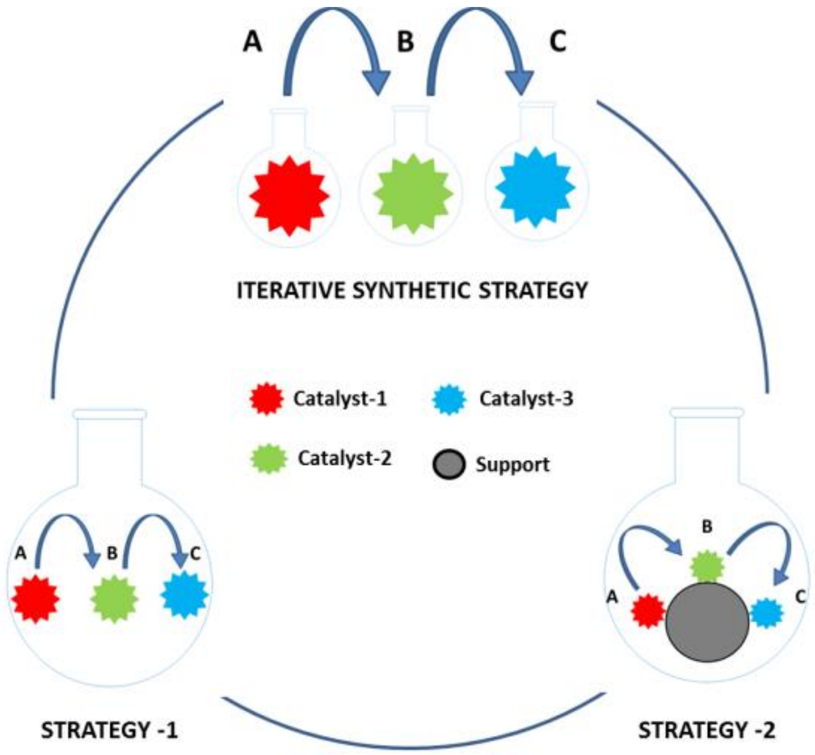
Table of Contents of the Executive Summary

Chapter 1

Introduction

1.1 Purpose

In the current era of organic synthesis, repetitive synthetic strategies are posing serious drawback. Therefore, there is a serious need to perform multi-transformations in a single reaction vessel, avoiding the isolation and purification at every stage. One such development is multi-catalysis in which multiple catalytic reactions are done in a single reaction vessel.



In multi catalysis system we can have two strategies: 1. there could be different catalysts in a single vessel acting conjunctionally or sequentially, 2. there could be multifunctional catalyst. Strategy-1 is not that lucrative as the isolation of the catalysts in pure form is sometimes not possible or a laborious one. Therefore strategy-2 is the preferential condition.

Strategy-2 involves co-immobilization of the two or more catalysts on the surface of the same support, resulting in a single catalytic material exhibiting many different catalytic properties.

To keep this objective in mind, we have developed tandem catalytic reactions to produce target products in a single step. For the purpose parameters like solvent system, temperature, stoichiometry of the reagent used and the amount of catalytic system were optimized. We have focussed on the development of methods involved in the synthesis of fine chemicals or pharmaceutical intermediates in a domino or tandem like catalysis processes. In a broad way these processes directly affect the atom economy and have a significant impact on the manufacturing of pharma intermediates and fine chemicals. Tandem reactions in which multiple reactions are combined into one step, in such process intermediates are not separated but allowed to transform into products or reactant for the next step. Due to these consecutive chemical processes, there is an overall saving of energy and unit operations in a chemical plant. The term tandem catalysis is broadly used in the literature that involves the sequential application of catalytic transformation with minimum or no work up or maintain the similar and mild reaction conditions. To carry out one pot tandem processes the special development of catalytic system is required by inducting multiple catalytic sites on a single support. The cooperative and synergistic action of all the catalytic centres require to carry out the tandem reaction successfully.

The development of a green one pot tandem catalytic process for the production of API, the following parameters should be taken care: (i) sufficient reaction site should be available on the surface of matrix (ii) there are chances of formation of by-products, during the different reaction steps should not interfere during the reaction or in the preceding steps (iii) there should be an immediate desorption of products from the surface and should not block the catalytic sites (iv) the product of the first step should easily available as a reactant for the second step and so on for the continuation of the tandem process (v) the selection of the solvent system for this tandem process is crucial and it should be compatible with all the reaction components, should be green in nature as well as recyclable (vi) the corrosion of the matrix and the leaching of the catalytic components should be monitored throughout the process. All these aspects can be set by process optimization. Overall, economic and ecological aspects should be considered for the development of the one pot multi-stage organic transformations on the industrial scale.

1.2 Research Methodology

- Synthesis of new catalytic systems.
- Characterization of the synthesized catalytic systems.
- Evaluation of the catalytic systems with respect to different substrates and different reaction conditions.
- Application of the said catalytic system.

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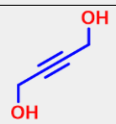
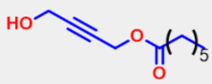
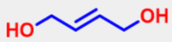
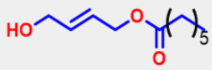
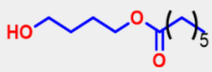
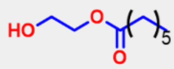
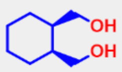
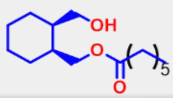
Chapter 2

Enzymatic Mono-esterification of Symmetric Diols: Restriction of Molecular Conformations Influences the Selectivity

2.1 Research Methodology

1,4-dihydroxy-2-butyne (400 mg, 4.64 mmol) was dissolved in diethyl ether (30 mL) at room temperature. Then, octanoic acid (669 mg, 4.64 mmol) was introduced and the reaction mixture was stirred for 5 min. Now, CALB (20 mg) was added and the solution was stirred with mechanical stirrer at 100 rpm for 24 h. After 24 h the reaction mixture was filtered to separate the enzyme. 30 mL water was added to the filtrate followed by addition of solid sodium bicarbonate in small portions till effervescence ceased. Aqueous layer was separated and discarded. The ether layer was initially washed with water (15 mL) and was distilled to give clear oil (500 mg, 2.35 mmol). The separated enzyme was recycled for three consecutive cycles without losing activity.

Selective esterification of heptanoic acid with diols having different levels of unsaturation and chain length under optimized conditions.[a]

Entry	Acid	Alcohol	Product	Monoester[c]	Yield %
1				91.25	71
2				93.0	66
3	Heptanoic acid			90.25	68
4				99.75	64
5				98.00	69

[a]Carboxylic acid (1 mmol, 1 eq), diol (1 eq.), enzyme (50 mg), Diethyl ether (50 mL). [b] isolated yield (mixture of monoester + diester only). [c] % of monoester present in isolated yield.

2.2 Key findings

We have experimentally demonstrated that by 'locking' the molecular conformation through the introduction of a double or triple bond in the center of a symmetric diol, enzymatic monoesterification can be achieved selectively. The enzyme Candida antarctica lipase B, generally used for the transesterification of diols, can be effectively used for the monoesterification of symmetrical diols in an unbuffered system also. By varying the chain length of a carboxylic acid moiety, we have established that optimum selectivity and efficiency can be achieved in the range of 4.8 to 5.0 pKa values. Selectivity can be improved up to 98.75% for a monoester in an overall 73% yield (mixture of a monoester and a diester) when but-2-yne1,4-diol reacted with hexanoic acid. Water, a by-product, provides an interfacial environment for the enzyme to work in the organic reaction medium. The uniqueness of the reported monoesterification protocol is that it involves only the mechanical stirring of the reaction mixture at room temperature in the presence of the enzyme for 24 h. High percentage yield with selectivity for a monoester, easier product isolation and overall, environmental sustainability are added advantages. The synthesized monoesters are characterized by using ^{1}H NMR and high-resolution mass spectrometry (HRMS).

2.3 Conclusion

Through this study we demonstrated that lipase category of enzymes like CALB can be used for esterification reaction too, besides transesterification for the production of monoester derivatives with higher percent selectivity. The by-product water formed during the reaction can tune the microenvironment around the catalytic lid of the enzyme mimicking the lipid/ water interfacial environment. This results in high % yield of the reaction. The lipophilicity of the enzymatic pocket as well as preference for stronger H-bonding should be the reason for preferential selectivity for a specific product. High selectivity can be achieved if molecular conformation of the diol can be locked. This study may provide a direction to future research in the field of molecular dynamic and docking to further support the observations. This process is suitable for the design of continuous flow reactor. By making few modifications and optimizing some parameters (e.g., thickness of the catalytic bed of immobilized enzyme, rate of diffusion, removal of by-product water at certain stage etc), diol and carboxylic acid can be set as inputs while the product monoester becomes continuous output from the reactor.

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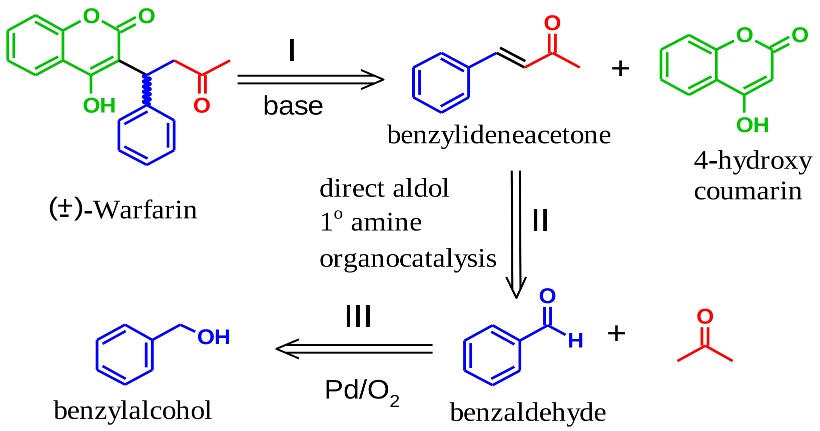
Chapter 3

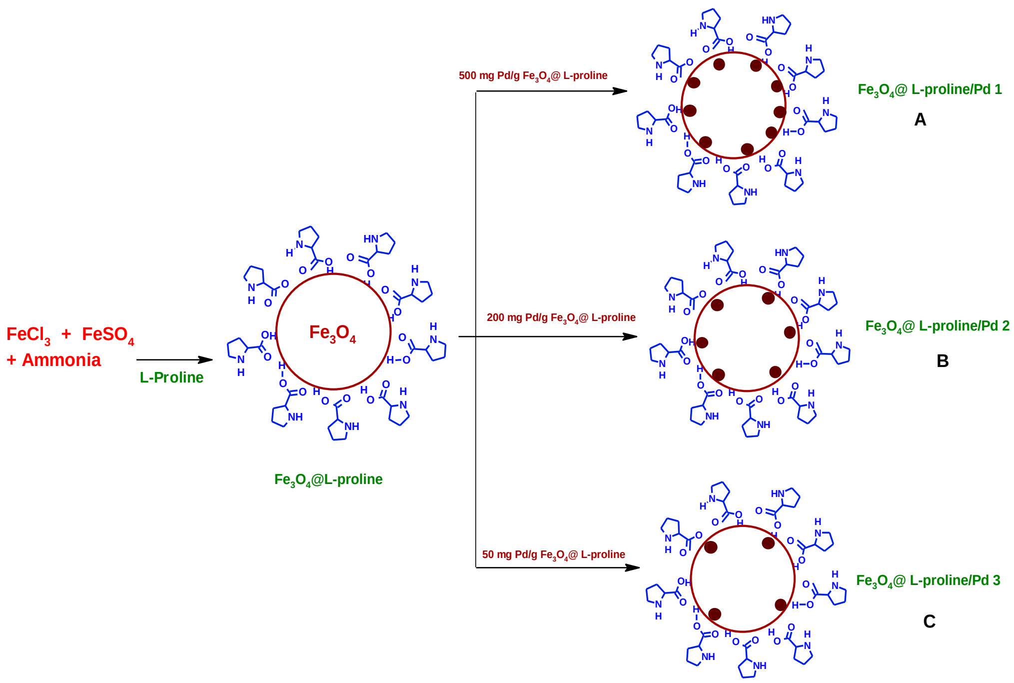
Fe_3O_4@L-proline/Pd Nanocomposite for One Pot Tandem Catalytic Synthesis of (±) - Warfarin from Benzyl Alcohol: Synergistic Action of Organocatalyst and Transition Metal Catalyst

3.1 Research Methodology

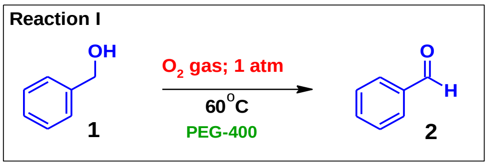
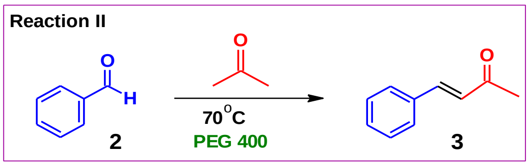


Planning for one pot synthesis of (±)-warfarin from benzyl alcohol through 3-way catalysis by using single nanocomposite catalyst having multiple components (I, II and III).

A 3-way catalysis is required for the one pot synthesis of (±)-warfarin from benzyl alcohol. The benzylideneacetone formed by α-alkylation of ketone with 1° alcohol in two steps can be directly condensed with 4-hydroxycoumarin under mild basic condition in a single pot. For the purpose, the amount of L-proline and Pd loaded on to the surface of host Fe_3O_4 must be optimized. Stoichiometric amount of L-proline was used as capping agent during the synthesis of Fe_3O_4 NPs. Hence, the amount of Pd loaded on the surface of Fe_3O_4@L-proline was varied. Accordingly, three sets of Fe_3O_4@L-proline/Pd NPs were prepared and used for optimization of alcohol/ketone condensation reaction leading to benzylideneacetone in one pot. The amount of Pd loaded was also determined from elemental EDAX analysis.



Reactions optimization in presence of as-synthesized catalytic nanocomposite having different amount of Pd loading.

Catalyst System	Amount of Pd mg/g NCs	Reaction I 	Reaction II 
A	500	Reaction completed in 32 h.	No reaction
B	200	Reaction completed in 60 h.	Reaction completed in 24 h.[a]
C	50	No reaction	Reaction completed in 20 h.

[a] ±0.5 h. The progress of reaction was monitored on TLC plate after every half an hour and the reactions were carried out in triplicate.

One pot synthesis of (±)-warfarin.

Benzyl alcohol (100 mg) was added to PEG-400 (5 mL) and stirred for 10 min. Then Fe_3O_4@L-proline/Pd 2 NCs (100 mg) was added and stirred for 10 min. The suspension was further stirred for about 60 h at 60 °C under 1 atmospheric pressure of dioxygen. After the disappearance of the starting material, flow of dioxygen was stopped and the reaction vessel was flushed with N_2 gas. To this reaction mass, acetone (5 mL) was introduced and stirred for 5 min under inert atmosphere. The reaction vessel was sealed with rubber septum and stirred at 70°C for about 24 h. Acetone was removed from the reaction mass under vacuum at 50°C. At this time, 4-hydroxycoumarin (75 mg) and water (5 mL) were added to the reaction mixture and stirred at 100°C. After stirring for 12 h the reaction mass was cooled to room temperature, the catalyst was removed magnetically. The product was filtered and recrystallized from acetone / water to give (±)-warfarin, (99 mg) as white solid having 35% overall yield from benzyl alcohol.

3.2 Key findings:

One-pot synthesis of (±)-warfarin, an anticoagulant, has been achieved from benzyl alcohol in a 'green way' by using a multicomponent catalyst. For the purpose, L-proline capped Fe_3O_4 nanoparticles (Fe_3O_4@L-proline NPs) were synthesized and metallic palladium was loaded on its surface (Fe_3O_4@L-proline/Pd NCs). The morphology, particle size and shape were studied by using FESEM and TEM analysis. The Pd present on the surface was responsible for oxidation of benzyl alcohol and its derivatives to the corresponding aldehyde in situ. This in turn, condensed with acetone to form the aldol condensation product, benzylideneacetone, at 70 °C due to the presence of the L-proline organocatalyst on the surface of Fe_3O_4 NPs. Later, 4-hydroxycoumarin was introduced to condense with in situ generated benzylideneacetone by a Michael addition to form the target product (±)-warfarin. It was established that benzyl alcohol can be converted into the final product, (±)-warfarin, with an overall 35% yield within 5 days in a single-pot process. This process requires a rise in temperature in stages to a maximum of 100 °C and 1 atm pressure of dioxygen gas. An important aspect of the developed process is the avoidance of loss of costly Pd by leaching and catalyst recovery by the use of a magnetic field. The use of a solvent like PEG400 makes the process green in a true sense. The interaction of L-proline with Fe_3O_4 NPs and the presence of Pd on the surface were confirmed by the FTIR and XRD patterns, respectively. The present study hereby suggests a combined 3-step mechanism for the production of the target product warfarin. Pilot-scale one-pot production of (±)-warfarin was carried out and a flow diagram with various unit processes is presented.

3.3 Conclusion

By implementing all the optimized process parameters for the pilot-scale production of (±) – warfarin, it can be concluded that (i) the developed process becomes cost effective compared to others based on bared noble metal catalysts (ii) the catalyst recovery becomes easy by applying magnetic field (iii) the possibility of noble metal leaching from NCs is nullified in the process as no strong base is used at any stage (iv) the as-synthesized catalyst NCs maintained its efficiency for three cycles (under this study) for 3-way catalysis (v) the reaction is 'green' as no noxious solvents are used and the whole one pot process can be carried out in PEG-400 and water as the reaction medium. This study opens new avenues for the development of multicomponent catalysts to produce materials on large scale in a 'green way'. The next study would be the development of tandem process for the large scale production of enantiopure warfarin by loading chiral 1^{o} diaryldiamines on the magnetic host surface with palladium.

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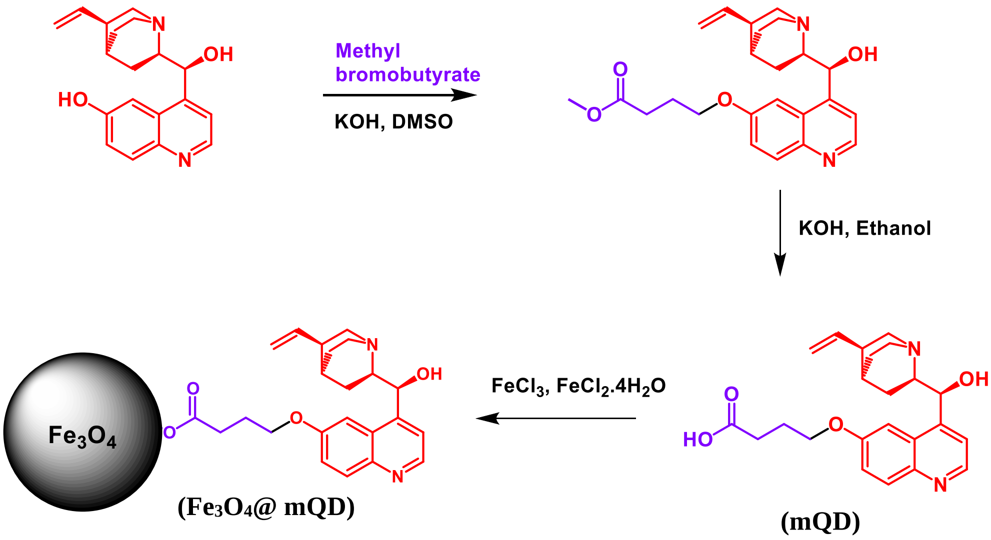
Chapter 4

Cinchona Alkaloid Derivatives modified Fe_3O_4 Nanoparticles for Enantioselective Ring Opening of *meso*- Cyclic Anhydrides

4.1 Research methodology

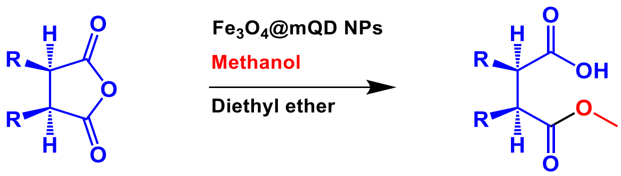


Preparation of modified quinidine supported on Fe_3O_4 magnetic nanoparticles (Fe_3O_4 @mQD NPs).

Supporting of 4-((4-((1S)-hydroxy((2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-yl)oxy)butanoic acid on *in situ* generated Fe_3O_4 magnetic nanoparticles (Fe_3O_4 @mQD NPs).

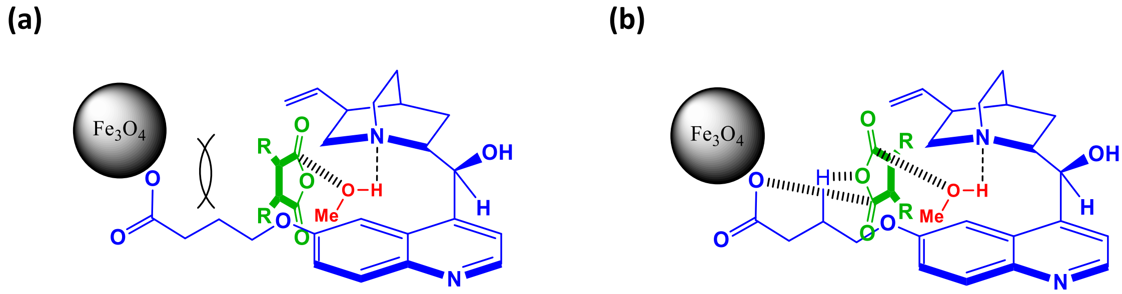
Modified quinidine m(QD) derivative coated magnetite nanoparticles were synthesized by the one-pot synthesis method. In brief, ferric chloride (1.42 g, 8.7 mmol) and ferrous chloride tetrahydrate (1.00 g, 5.02 mmol), molar ratio 1.75:1, respectively were added to 50 mL deionized water in an inert atmosphere. The mixture was heated to 70 °C to obtain a clear yellow solution. The mixture was stirred vigorously with a mechanical stirrer to avoid interparticle magnetic interaction. After 30 min, modified quinidine (mQD) (7.97 g, 20.1 mmol), dissolved in deionized water (25 mL) was rapidly added. The solution was further cleared by the addition of conc. HCl (7 mL) and stirred for another 30 min. Then 20 mL ammonia solution (about 25% in water) was rapidly added. The reaction color was changed to black. The stirring was continued for 1.5 h. Finally, the black nanoparticles were separated magnetically, washed with distilled water (200 mL) three times, and washed with methanol (200 mL) three times, then dried in an oven at 100 °C overnight. Dry weight of nanoparticles: 1.2 g

Fe_3O_4 @mQD NPs - catalyzed ERO of different meso-cyclic anhydride.



General procedure for Fe_3O_4@mQD NPs mediated ring opening of *meso*-cyclic anhydride.

Methanol (10.0 mmol) was added dropwise to a stirred suspension of the anhydride (1.0 mmol) and the Fe_3O_4 @mQD NPs (100 mg) in diethyl ether (5.0 mL) at -45 °C under argon. The reaction mixture was stirred at this temperature for 60 h. During this period, the anhydride gradually dissolved. Subsequently, the catalyst is separated by applying a magnet and the resulting clear solution was concentrated *in vacuo* to dryness, resulting in the corresponding monoester.



Proposed different ways of spatial arrangements of *meso*-cyclic anhydride at the catalytic cavity to minimize the steric and prevent the protonation of the catalytic center. It is proposed that orientation 'b' is favored in the present case.

4.2 Key findings

In the present work, the molecular framework of quinidine was modified at the methoxy functional group of the C60 carbon of the quinoline moiety with a long-chain carboxylic acid group (–COOH) and it was used as a capping agent during the synthesis of Fe_3O_4 NPs. The resulting modified quinidine capped Fe_3O_4 (Fe_3O_4@mQD) NPs were characterized by different techniques and used for enantioselective ring opening (ERO) by methanolysis in a heterogeneous mode of catalysis. The interactions of mQD with the Fe_3O_4 surface, as well as its % loading, were studied using FTIR spectroscopy and thermal analysis techniques. Reaction parameters like the solvent system, temperature, and substrate were optimized. ERO of succinic and glutaric anhydrides by methanolysis was carried out in the presence of Fe_3O_4@mQD NPs. The optimized protocol can produce a chiral hemiester with high enantioselectivity (up to 98% ee) and excellent % yield (more than 90% in most of the cases).

4.3 Conclusion

We have demonstrated that the enantioselective *meso*-cyclic anhydride ring opening by alcoholysis can be carried out in a highly efficient and selective way by systematic modification in the cinchona alkaloid's molecular framework and by adsorbing the same on the surface of magnetic Fe_3O_4 NPs to ease the recovery and recycling of the catalyst. The optimization of reaction parameters of model ERO by alcoholysis establishes that the developed protocol results up to 97% yield with 98% ee of chiral hemiester when the reaction is carried out at -45 ^{o}C in diethyl ether as a solvent for 60 h in the presence of a catalytic amount of Fe_3O_4@mQD NPs. By implementing all the optimized process parameters for pilot-scale production of chiral hemiester, it can be concluded that (i) the developed process becomes cost-effective compared to other processes due to the requirement of less amount of catalyst (ii) catalyst recovery becomes easy by applying a simple bar magnet (iii) the problem of protonation of catalytic quinidine nitrogen by the product hemiester gets nullified due to proper molecular orientation of QD on adsorption keeping the distance between catalytic site, substrate and the product formed (iv) the as-synthesized catalyst NPs maintained their efficiency for five cycles without significant loss in % yield and selectivity. Absorption and emission spectroscopies, chiroptical study, and surface probe microscopy revealed that spatial molecular orientation of the chiral molecule on adsorption could induce a proper molecular orientation by intermolecular hydrogen bonding, in turn, making the achiral magnetic surface chiral. These chirality-induced magnetic surfaces can be exploited for enantioselective organic transformations. This study opens new avenues for the development of chiral magnetic surfaces that can be used for efficient stereoselective heterogeneous catalysis.

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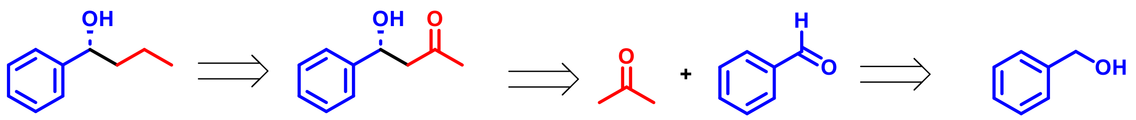
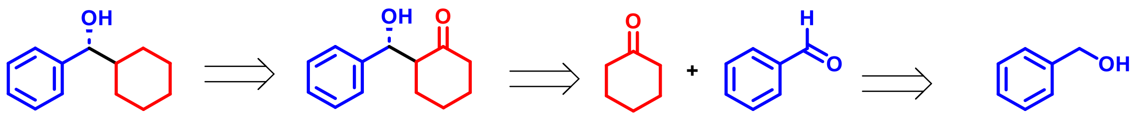
Chapter 5

One pot Synthesis of Pharmaceutically useful Chiral intermediate by using Multi-catalytic System

5.1 Research methodology:





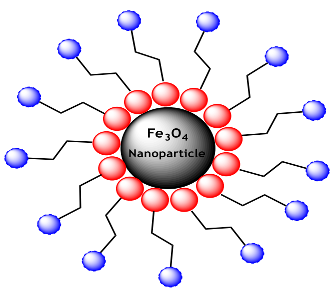
Retro synthetic analysis of the substituted chiral benzyl alcohols

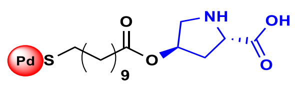
For this purpose, a catalytic system is required which should contain an element by which oxidation of benzyl alcohol to benzaldehyde under oxygen atmosphere. The catalyst should contain a catalyst which should support the enantioselective aldol reaction. The catalytic system should withstand the reaction condition of Wolff Kishner reduction. The catalytic system should be magnetic so the after the reaction it can be completely recovered by magnetic separation.

For this, we have developed mPr@Pd@Fe_3O_4 nanocomposite (NCs) and used it as single catalyst for the proposed tandem process beginning from benzyl alcohol. The process parameters like temperature, reaction time, solvent and the stoichiometry of the reagents required at each stage are optimized considering the environmental aspects.

Preparation of mPr@Pd@Fe_3O_4 catalyst.

To a 2000ml round bottom flask, which was flushed argon gas previously, was charged with Palladium acetate (368 mg), disulfide derivative of proline (600 mg) and dehydrated DMSO (820 mL) was added, keeping in argon atmosphere. To the clear bright yellow solution, was added Fe_3O_4 NPs (300mg) and stirred for 10 minutes. To this suspension, sodium borohydride solution (680 mg) in MeOH (60 mL)) was dropped over 1 h and the resulted black suspension was stirred at room temperature for 24 h. During the working up, the black solid component was decanted, washed with EtOH (400 mL), AcOH (400 mL), EtOH (1000 mL), Et_2O (200 mL), respectively, and dried in vacuum at room temperature to give mPr@Pd@Fe_3O_4 as a black solid (320 mg).





General procedure for the preparation of chiral aldol products:

To the solution of benzyl alcohol 1.08g (10 mmol) in PEG-400 (2ml) was added mPr@Pd@Fe_3O_4 catalyst (150mg) and the resulting mixture was stirred at 40°C under about 1 atmospheric pressure of oxygen till reaction complies on TLC or no starting material is left. Reaction mixture is then cooled to room temperature, oxygen atmosphere is removed and acetone 8 ml is added to the reaction mixture. The reaction mass was stirred at 40^oC till reaction complies on TLC or no aldehyde is left. Acetone was removed under vacuum and the residue was purified with column chromatography using 30% Ethyl acetate in Hexane as eluent.

5.2 Key findings

In this chapter we have synthesized Chiral alpha propyl benzyl alcohol, in one pot starting from benzyl alcohol. The sequence includes oxidation of benzyl alcohol followed by aldol reaction catalysed by a multi catalytic system. Further the aldol product is converted to the alpha propyl benzyl alcohol via modified Wolff Kishner reduction.

For this purpose, a catalytic system is required which should contain an element by which oxidation of benzyl alcohol to benzaldehyde under oxygen atmosphere. The catalyst should contain a functional group which should support the enantioselective aldol reaction. The catalytic system should withstand the reaction condition of Wolff Kishner reduction. The catalytic system should be magnetic so that after the reaction it can be completely recovered by magnetic separation.

For this, we have developed mPr@Pd@Fe_3O_4 nanocomposite (NCs) and used it as single catalyst for the proposed tandem process beginning from benzyl alcohol. The process parameters like temperature, reaction time, solvent and the stoichiometry of the reagents required at each stage are optimized considering the environmental aspects.
The developed mPr@Pd@Fe_3O_4 nanocomposite (NCs) were characterized by TEM, elemental distribution with TEM, IR spectroscopy and surface area analysis.

5.3 Conclusion

The prepared catalyst mPr@Pd@Fe_3O_4, is useful for the synthesis of substituted chiral benzyl alcohols and can be used many times without losing its activity. The magnetic support assists the easy recovery after the reaction.

5.4 Biblography

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