A SYNOPSIS

of the thesis

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

To be Submitted

As a partial fulfilment for the award of the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

By

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Under the supervision of

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Synopsis

of the thesis

To be submitted to The Maharaja Sayajirao University of Baroda

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DOCTOR OF PHILOSOPHY in Chemistry

Name of Student: Sanjivkumar Tomer

Title of the Thesis: Synthesis and Characterization of Catalytic Materials and their application in Organic Transformations

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Synopsis

The Thesis will be presented in form of the following chapters:

Chapter 1

Introduction

Chapter 2

Enzymatic Monoesterification of Symmetric Diols: Restriction of Molecular Conformations Influences Selectivity

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

Chapter 4

Enantioselective Ring Opening of Meso- Cyclic Anhydrides by Fe_3O_4@mQD Nanoparticles: Inducing Chirality on Achiral Magnetic Surfaces by Modified Cinchona Alkaloid Derivatives

Chapter 5

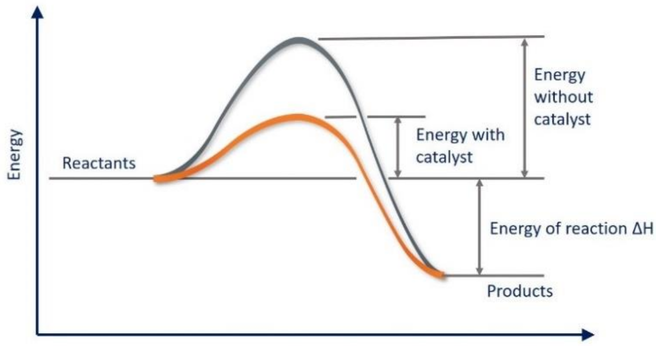
One pot Synthesis of Pharmaceutically useful Chiral intermediate, by using Multi-catalytic System

Synopsis

Chapter 1

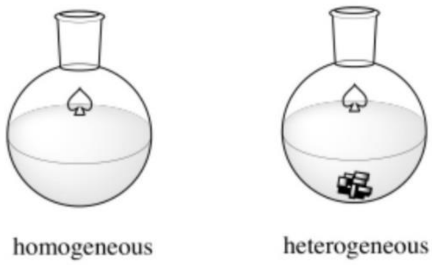
Introduction

Catalyst is a substrate which increase the rate of reaction without itself getting consumed.



Catalysts are mainly of two types: **heterogenous and homogeneous**.

In heterogeneous the catalyst is in different phase from the reaction medium while the homogeneous the catalyst is in the same phase of the reaction medium. If we look closely, in homogenous catalysis both the reactant and catalyst are in the same phase and is more efficient as the catalyst is having high interaction with the substrate. But at the end of the reaction, it is very difficult to isolate the homogeneous catalysts.



The heterogenous catalyst is having an advantage of ease of separation from the reaction medium by simple technique like filtration.

As like the homogeneous catalysts, the heterogeneous catalysts are not evenly distributed in the reaction medium and have limited catalytic sites for the substrate. The rate of reaction is directly proportional to the catalytic sites or surface area. Therefore, the surface area of the heterogenous catalysts is increased either by loading on some inert material or reducing the particle side.

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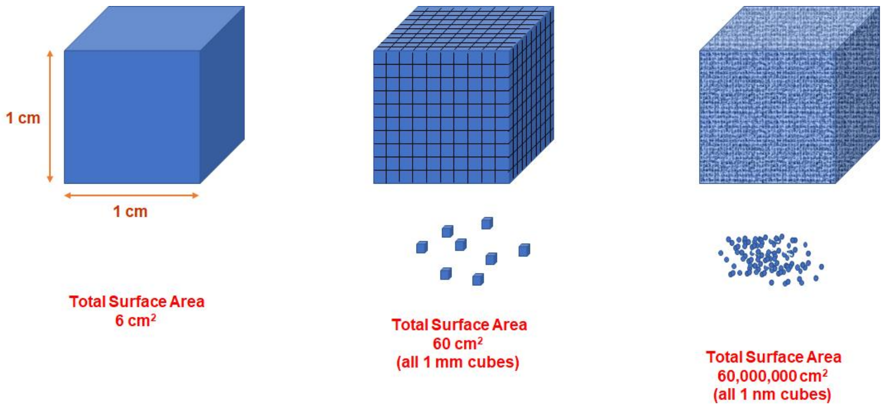
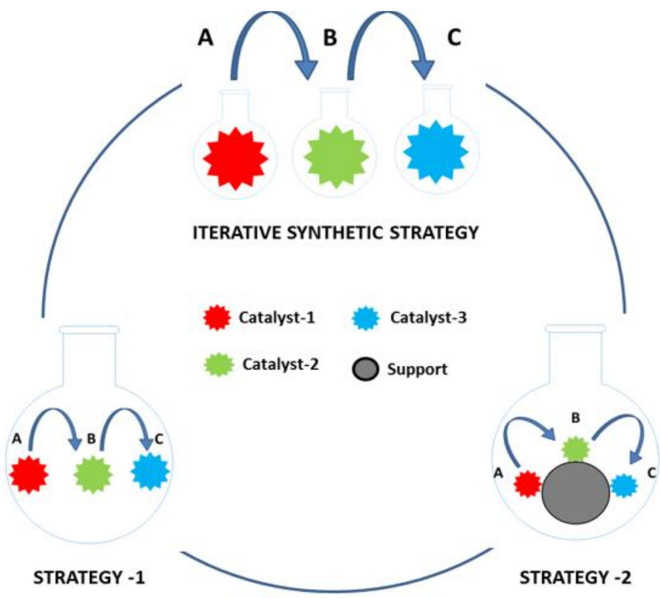
When the particle size of the catalyst is reduced to nano scale, the science dealing with this is known as Nanoscience or nanotechnology. Nanoparticles are of extreme interest for the loading of the catalysts. Due to their high surface area the loading of the catalyst is found to be high as compared to the other supports. The reaction rates are high as compared to the normal catalyst as most of the catalytic sites are exposed and accessible to the substrate.



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.



Synopsis

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. Scenario 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.

The chapter 1 include the updated literature survey in the subject of the thesis.

In the current work we have the following objectives:

- 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.

Chapter 2

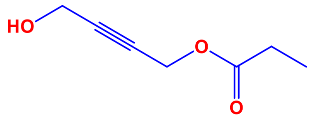
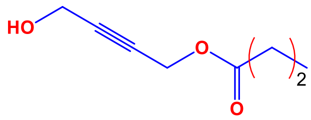
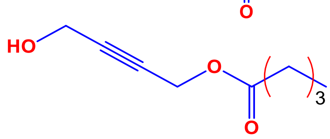
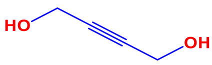
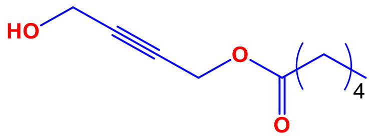
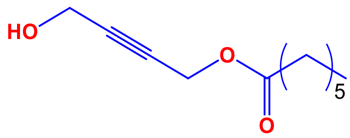
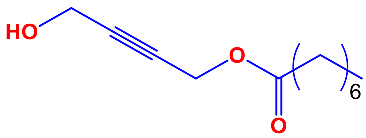
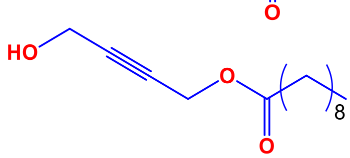
Enzymatic Mono-esterification of Symmetric Diols: Restriction of Molecular Conformations Influences Selectivity

Esterification is one of the most important reactions in organic synthesis. Organic esters find applications in diverse areas. For example, the fatty acid monoester and diester of 1,3-propanediol are useful in the production of soaps, detergents, shampoos, cosmetics, as well as several industrial applications. In these products, they find application as surfactant, emulsifier, dispersants, corrosion inhibitors, lubricants, demulsifiers, and so on.[1] However, the reaction is governed by equilibrium and as it proceeded in the forward direction, the reverse reaction i.e. hydrolysis of ester also compete, affect overall reaction yield. If water produced during the process is removed continuously using the simple apparatus like 'Dean and Stark', the reaction can be shifted to forward direction to almost completion.[2, 3] In most of the cases the reaction is carried out in excess of alcohol as a medium and catalysis by mineral acid is a routine practice. However, this simple procedure is not applicable for the monoesterification of symmetrical diol having both hydroxyl groups chemically equivalent.[4-8]

In past, many methods were specifically developed for the selective mono-functionalization of 1,n-diol. These methods were innovative and highly contributed to the development of the field. But, these protocols use some specialty reagents or solvents which may difficult to handle. Solvent recovery during process is harmful to the environment on exposure or when applied for large scale production.

We had carried out esterification (a test reaction) of but-2-yne-1,4-diol with heptanoic acid in diethyl ether as a medium in absence of enzyme at room temperature for 24 h, but the reaction was not proceeded at all confirmed by Thin Layer Chromatography (TLC) analysis. To optimize the reaction parameters we fixed the diol (but-2-yne-1,4-diol) and carried out the reaction with carboxylic acid having different chain length in presence of CALB enzyme in organic reaction media (Table 1).

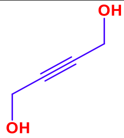
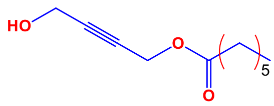
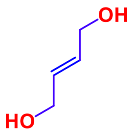
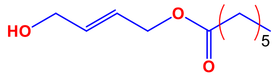
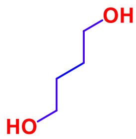
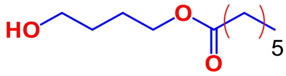
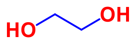
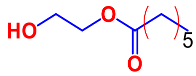
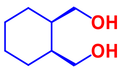
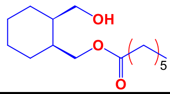
Table 1. Selective esterification of but-2-yne-1,4-diol with carboxylic acids having different chain length under optimized conditions.[a]

Entry	Alcohol	Acid	Product	Monoester[c]	Yield[b] %
1		Formic acid	No reaction	--	--
2		Acetic acid	No reaction	--	--
3		Propionic acid		92.0	64
4		Butyric acid		94.75	61
5		Pentanoic acid		92.75	62
6		Hexanoic acid		98.75	73
7		Heptanoic acid		91.25	71
8		Octanoic acid		97.5	62
9		Decanoic acid		88.0	45

[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.*

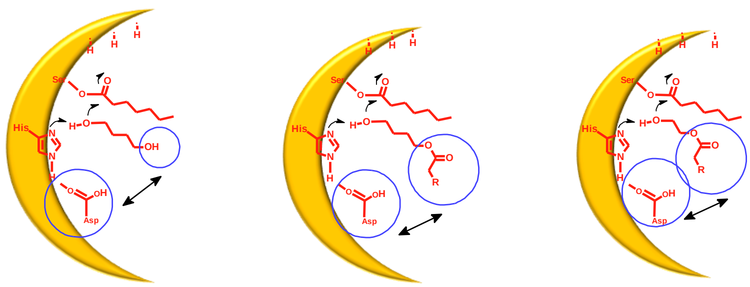
From this study we observed that hexanoic and heptanoic acid are the perfect match for the reaction with high selectivity and yield for mono-esterification. Therefore, for mono esterification of different diols we designed next set of experiments in which heptanoic acid was selected as a substrate and type of diol varied (Table 2). In the earlier discussion we proposed that the conformation of diol directly affects the fate of reaction. Hence, we selected symmetrical diols with different levels of unsaturation at the centre to arrest the molecular conformation and stabilize the same through H-bonding in the catalytic pocket (Scheme I).

Table 2. 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 %[b]
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.*

Proposed scheme I explains the performance for high selectivity for monoester product. These diol molecules can very well accommodate and stabilize in the catalytic pocket by H-bonding with Asp oxygen atom (Scheme Ia). The same is the case with cyclic aliphatic diol, (Entry 5). The monoester accommodated in the catalytic groove cannot be stabilized due to steric hindrance with Asp residue (Scheme Ib) and steric hindrance is the most effective in case of monoester of ethane-1,2-diol (Scheme Ic) explains high selectivity.



(a) No hinderance (b) hinderance (c) Maximum hinderance

Scheme I. Proposed steric hindrance between monoesters and Asp residue in the catalytic groove explains high selectivity for monoester of ethane-1,2-diol.

Synopsis

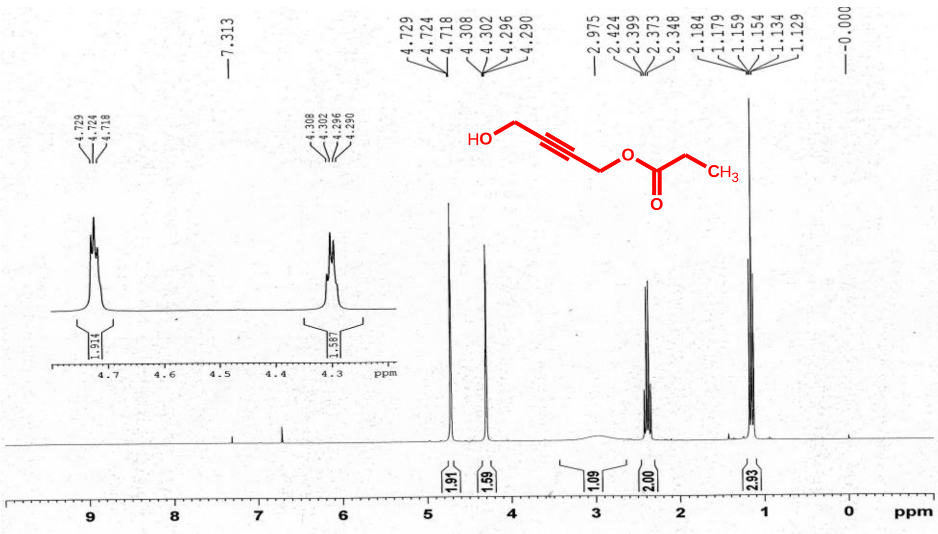


Figure 1: HNMR of 4-hydroxybut-2-yn-1-yl propanoate

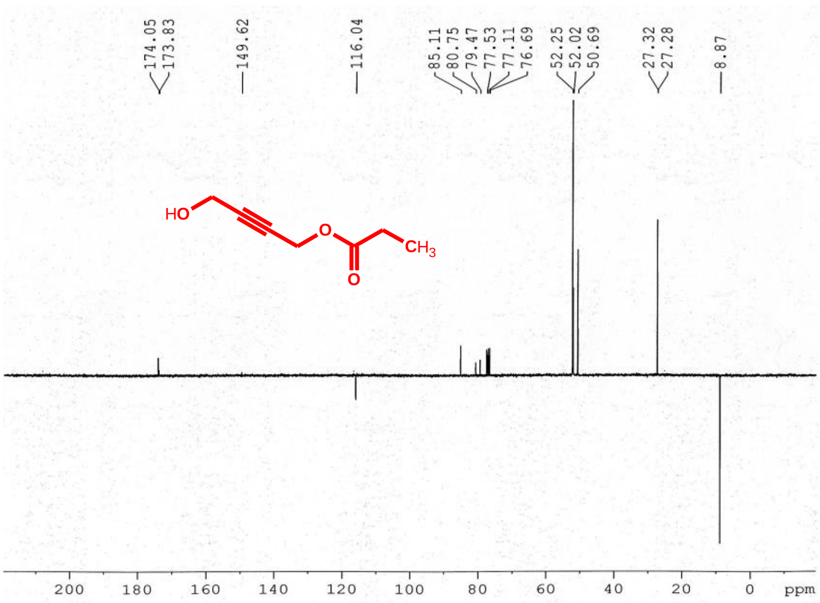


Figure 2: APT of 4-hydroxybut-2-yn-1-yl propanoate

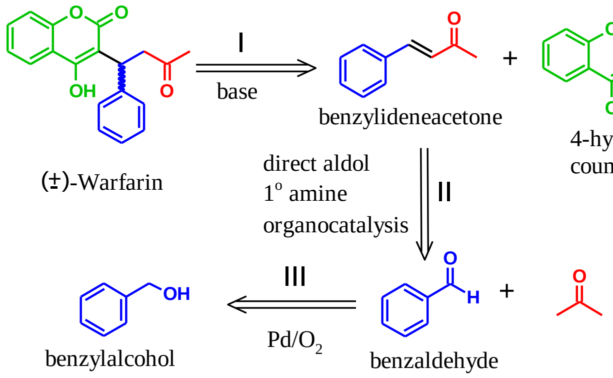
Conclusion: Through this study we demonstrated that lipase category of enzymes like CALB can be used for esterification reaction too, besides transesterification for the production of monoester derivatives with higher percent selectivity High selectivity can be achieved if molecular conformation of the 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.

Chapter 3

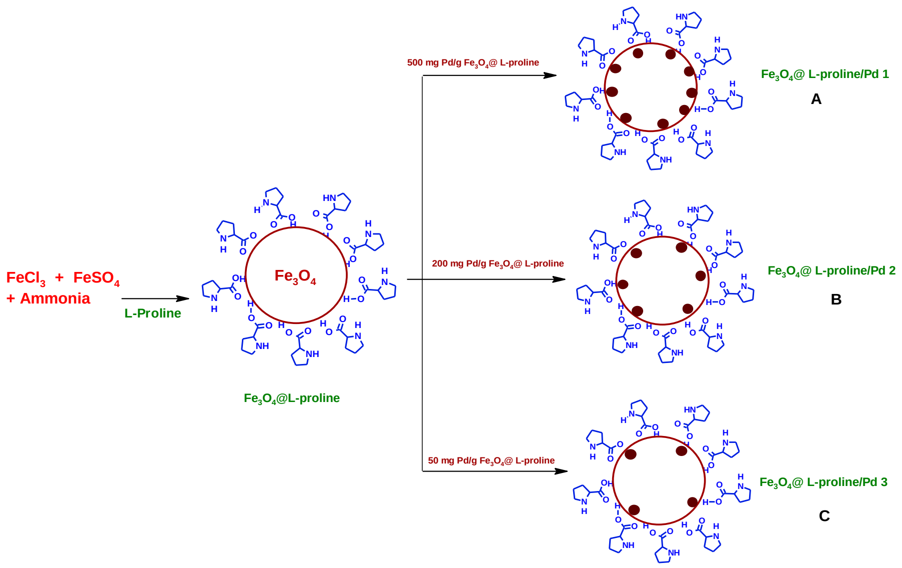
Fe_3O_4@L-Proline/Pd nanocomposite for one-pot tandem catalytic synthesis of (±)-warfarin from benzyl alcohol: synergistic action of organocatalyst and transition metal catalyst

Introduction:

Warfarin (Coumadin® or Marevan®) is an anticoagulant drug most commonly prescribed by physicians for the prevention of thrombosis and embolism. The purpose of this work is to develop a tandem one-pot catalytic process involving a cascade of chemical reactions carried out by using 'green solvents and reagents' leading to racemic warfarin. For this, we have developed Fe_3O_4@Lproline/Pd 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.



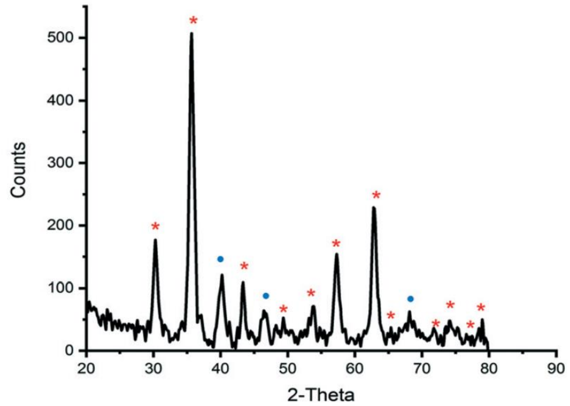
Preparation of catalyst:



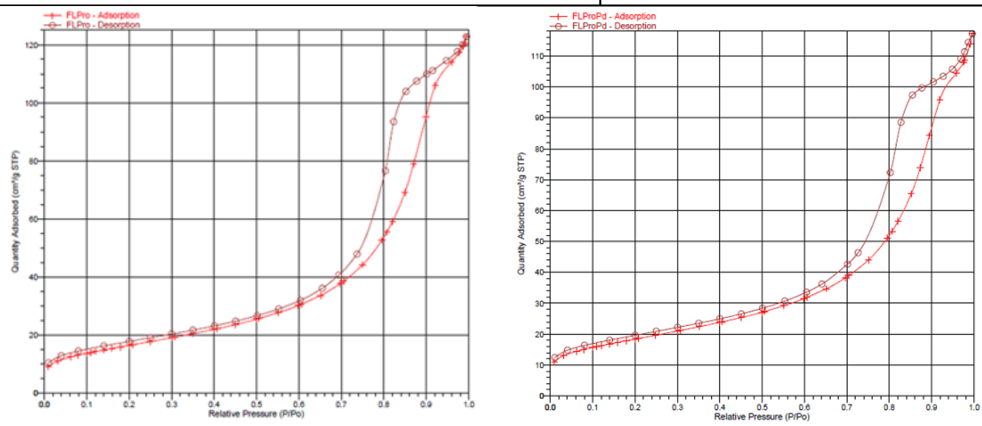
Stoichiometric distribution of Pd metal on surface of L-proline capped Fe_3O_4 NPs

Synopsis

Characterization:

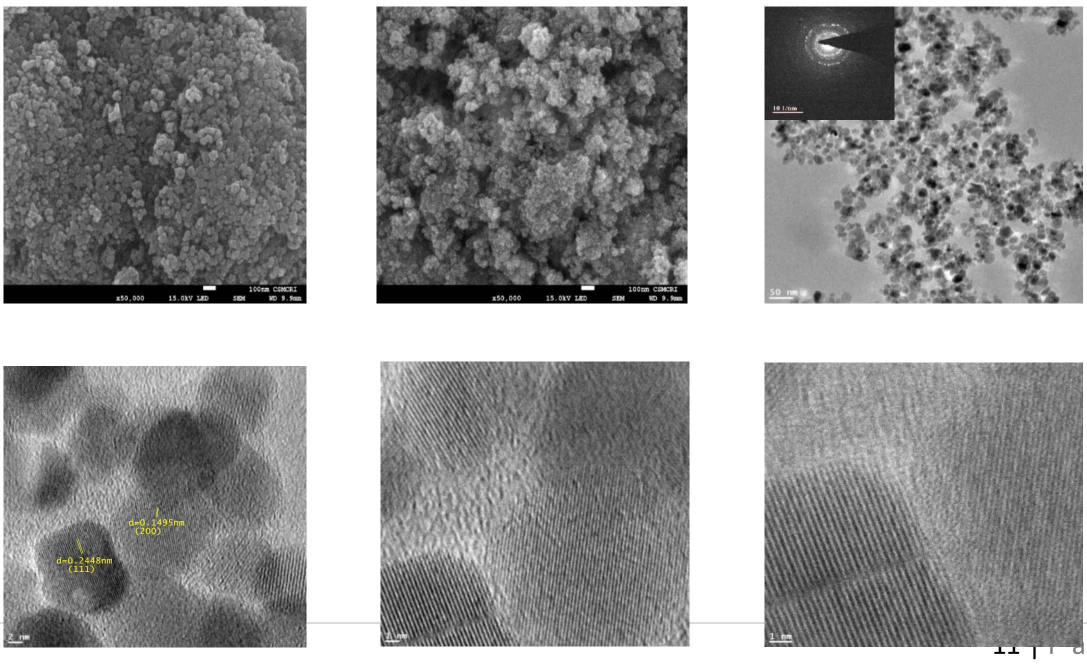


XRD pattern of Fe_3O_4@L-proline/Pd NCs (* and • indicate Fe_3O_4 and Pd respectively). The XRD pattern manifests predominant diffraction peaks at 2θ values of 30.51°, 35.78°, 43.55°, 47.13°, 53.50°, 57.40°, 62.92°, 65.74°, 70.92°, 73.96°, 74.96° and 78.92° corresponding to the (220), (311), (400), (331), (422), (333),(440), (531), (620), (533), (622) and (444) planes respectively (JCPDS 82-1533), confirming the magnetite phase of inverted spinel structure having a face centered cubic (FCC) arrangement and Fe cations occupying the interstitial Td and/or Oh sites.



Nitrogen adsorption–desorption isotherms for Fe_3O_4@L-proline and Pd loaded Fe_3O_4@L-proline

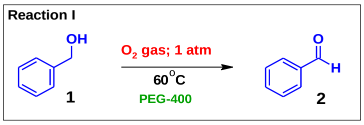
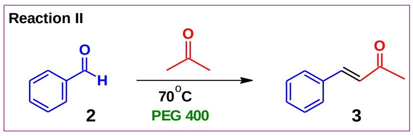
Sr. No.	Parameters	Fe_3O_4@L-proline NPs	Fe_3O_4@L-proline/Pd NCs
1	S_{BET} (m^2/g)	59.39	65.23



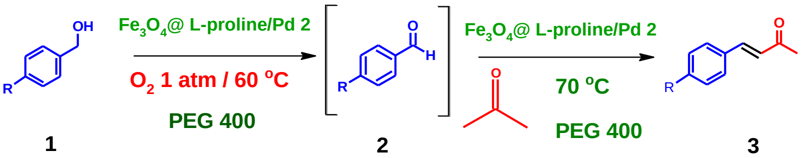
FESEM image (before Pd loading) (E) FESEM image (after Pd loading) TEM image (inset image shows SAED pattern) and Lattice fringes at higher magnification of as-synthesized Fe_3O_4@L-proline/Pd NCs

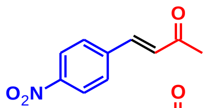
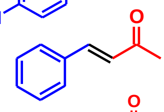
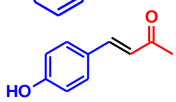
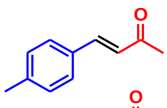
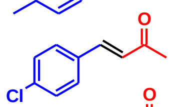
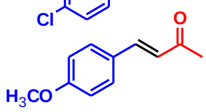
Synopsis

Reaction optimization in the presence of as-synthesized catalytic nanocomposite having different amounts of Pd

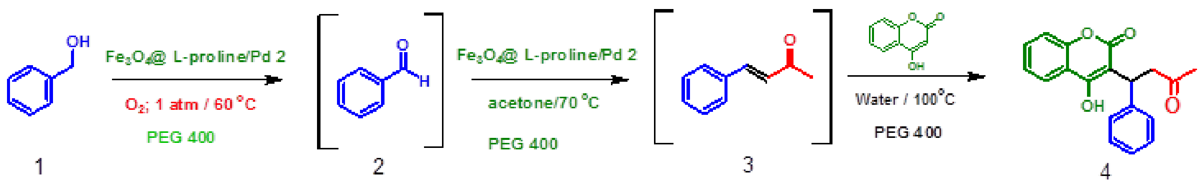
Catalyst System	Amount [b] of Pd mg/g NCs		
A	500	Reaction completed in 32 h.	No reaction
B	200	Reaction completed in 60 h.	Reaction completed in 24 h.[c]
C	50	No reaction	Reaction completed in 20 h.

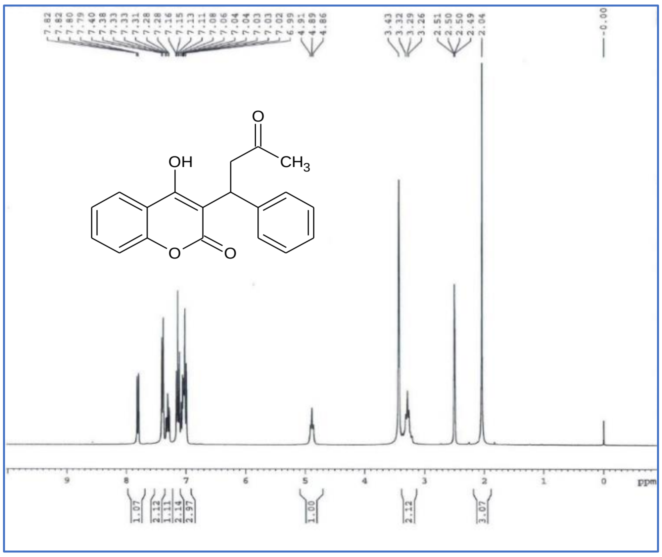
One-pot conversion of benzyl alcohol and its derivatives to benzylideneacetone in the presence of Fe_3O_4@L-proline/Pd NCs under optimized reaction parameters

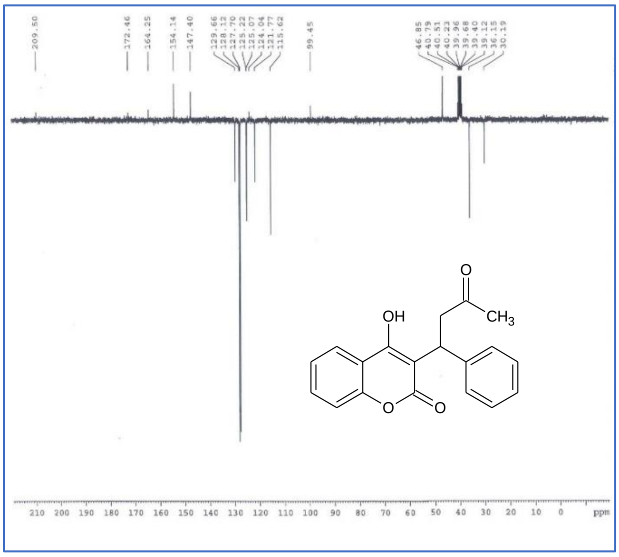


Sr. No.	-R	Time (h)	Expected product	Yield (%)
1	$-NO_2$	60 + 24		No product
2	-H	60 + 24		47
3	-OH	60 + 24		No product
4	$-CH_3$	60 + 24		52
5	-Cl	60 + 24		52
6	$-OCH_3$	60 + 24		58

Synthesis of (±)-warfarin through 3-way catalysis in the presence of Fe_3O_4@L-proline/Pd







1H NMR and 13C NMR of Warfarin

Conclusion: We have demonstrated that multi-step synthesis of pharmaceutically important molecules can be carried out in a single pot by inserting multiple catalytic components into a robust host and optimizing the reaction parameters.

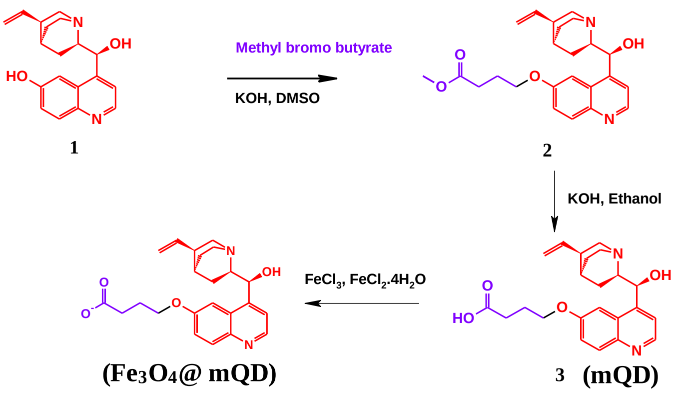
Chapter 4

Enantioselective Ring Opening of Meso- Cyclic Anhydrides by Fe_3O_4@mQD Nanoparticles: Inducing Chirality on Achiral Magnetic Surfaces by Modified Cinchona Alkaloid Derivatives

Introduction

Enantioselective meso-cyclic anhydride ring opening or desymmetrization of cyclic anhydride is one of the most important protocols in the field of asymmetric synthesis.[9-13] It allows the direct accesses of product with multiple stereocentres in a single step with high stereoselectivity (almost 99% ee) and yield.[14] Due to this protocol, many steps (eg. protection-deprotection of essential functional groups) and precious chiral auxiliaries involved in a total synthesis can be saved.

This work aims to create a chiral surface by chemisorbing the asymmetric molecules from the cinchona alkaloid class. It would be interesting to study the fate of ERO by alcoholysis to form chiral hemiester when carried out over such chiral surfaces. Fe_3O_4 NPs are the most suitable materials for the surface modification and the ease of chiral catalyst's recovery and recycling. Literature survey shows that most of the ERO by alcoholysis is carried out in the presence of quinidine, a member of cinchona alkaloid class, as a catalyst. From the structural point of view, it is meaningful to exploit $-OCH_3$ group attached at C6' of quinoline ring of quinidine to make the molecule suitable for surface adsorption and take advantage of whole cinchona molecular framework for chiral induction (Fig. S1) But the main hindrance is the short chain-length of the $-OCH_3$ group, which makes it unsuitable for surface interactions. Instead, the carboxylic acid group is the most suitable to interact with the surface Fe^{2+}/Fe^{3+} ions either in monodentate or bidentate modes. Considering these aspects, $-OCH_3$ group at C6' is replaced by $–O(CH_2)_3COOH$ group to induce the flexibility at the end (Scheme 1). The final modified quinidine derivative **3** (mQD) acts as a capping agent during the synthesis of Fe_3O_4 NPs.



Scheme 1. Preparation of modified quinidine supported on Fe_3O_4 magnetic nanoparticles (Fe_3O_4 @mQD NPs).

The developed catalytic system has an added advantage of heterogeneous catalysis and easy recovery at the end of reaction through magnetic separation.

(a)

(b)

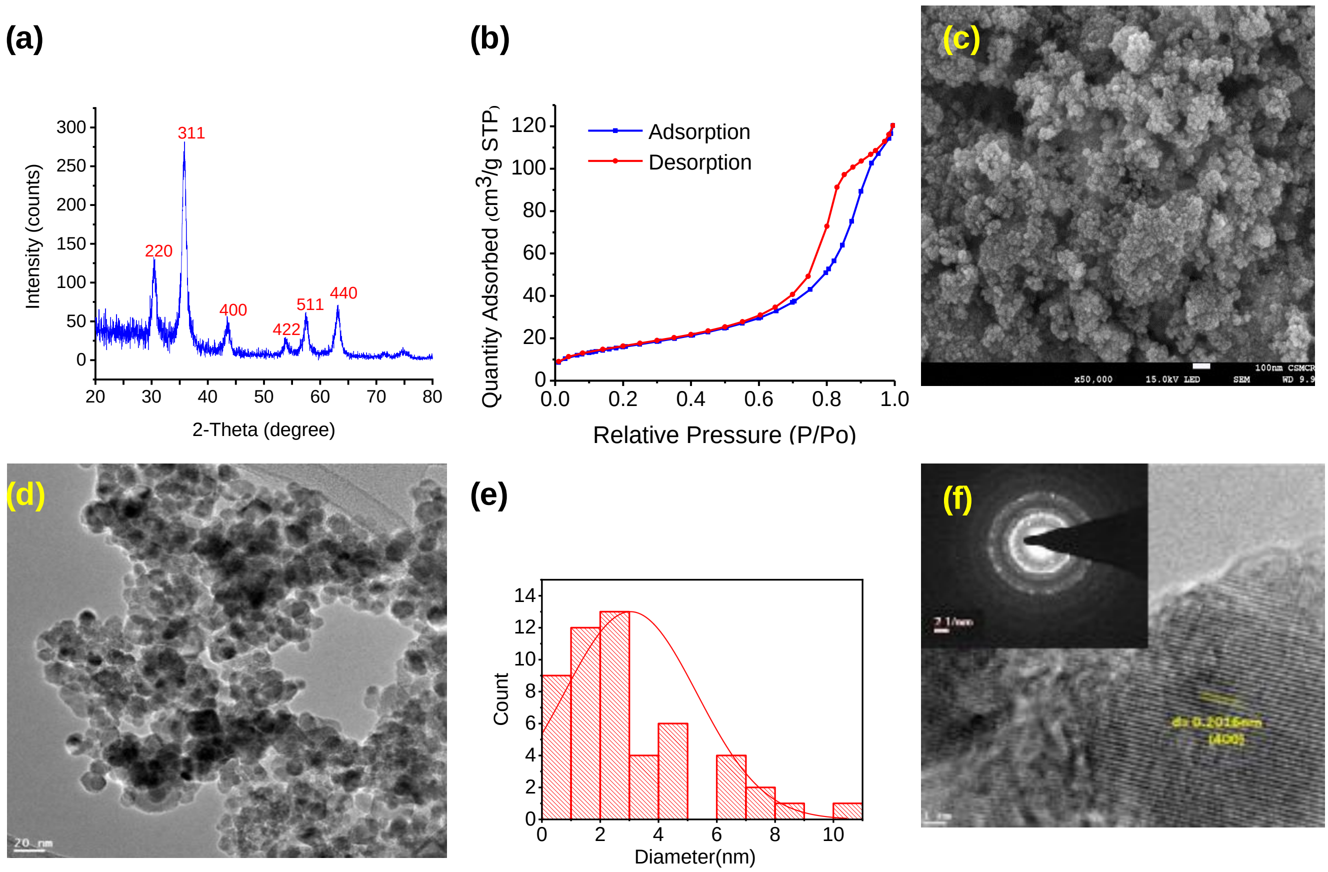
Fig. 1. a) Reaction mixture of Anhydride, Methanol and Fe_3O_4@mQD NPs under stirring with magnetic bar **b)** reaction mixture when magnetic stirring is stopped and the catalyst sticks to the magnetic needle.

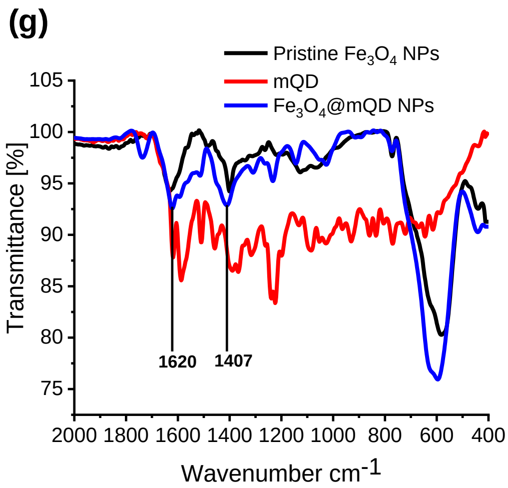
Results and discussion

The synthesized Fe_3O_4@mQD NPs were characterized by powder XRD to check the material's phase purity, particle size and crystallintiy. The X-ray diffraction peaks at 2θ values of 31.5, 36.2, 43.7, 53.4, 57.5 and 63.0° correspond to the (220), (311), (400), (422), (511) and (440) planes, respectively (JCPDS no. 82-1533), confirming the magnetite phase of Fe_3O_4 NPs with inverted spinel structure (Fig. 1a). The particle size was calculated by Debye-Scherrer formula ($L=0.9\lambda/\beta\cos\theta$) [15] and the FWHM (Full Width at Half Maximum) value of the major peak for (311) planes is in the range of 22.73 nm. XRD pattern remains unaltered on surface adsorption of mQD. The nitrogen adsorption–desorption isotherms for the synthesized Fe_3O_4@mQD NPs, is presented in Fig. 2b. It can be observed from Fig. 2(b) that the isotherms of Fe_3O_4@mQD NPs are almost similar to that of type IV (BDDT classification) with the H4 type of hysteresis loop in which the two branches are nearly horizontal and parallel over a wide range of relative pressures (P/Po). In this case, the quantity of gas adsorbed increases with increase in P/Po. The type H4 loop is often associated with narrow slit-like pores.[16,17] The adsorption average pore width (4 V $Å^{-1}$ by BET) values indicate a mesoporous material. The BET surface area and pore size studies reveal that the material is suitable for catalytic activities.

The structure and morphology of the sample were observed directly by Field Effect Scanning Electron Microscopy (FESEM) and Transmission Electron Microscopy (TEM) (Fig. 2c-f). It can be observed from Fig. 2 that Fe_3O_4@mQD NPs manifest spherical morphology in a size range of 2 -10 nm. The highly crystalline nature of the material is confirmed from the Selected Area Electron Diffraction (SAED) pattern. The lattice fringes of the exposed planes (400) are spaced between 0.20 nm distances.

FTIR spectroscopy is one of the best tools to study ligand molecules' interactions with the host surface.[18-20] Figure 2g shows the FTIR spectra of mQD and Fe_3O_4@mQD. The vibrations at 1590 and 1430 cm^{-1} correspond to ν_{as} and ν_s carboxylate stretching in free mQD. On coordination with surface Fe^{2+}/Fe^{3+} ions, the ν_{as} increases to 1620 cm^{-1} while that of ν_s decreases to 1407 cm^{-1}. On comparing Δ ($\nu_{as(COO^-)}$ - $\nu_{s(COO^-)}$) with Δ' ($\nu'_{as(COO^-)}$ - $\nu'_{s(COO^-)}$), $\Delta < \Delta'$ was established (where Δ indicates the difference in the absorption bands for pristine Fe_3O_4 NPs while Δ' indicates the same for Fe_3O_4@mQD) suggesting monodentate coordination of carboxylate ions of mQD with the surface Fe^{2+}/Fe^{3+} ions under the conditions of chemical synthesis.





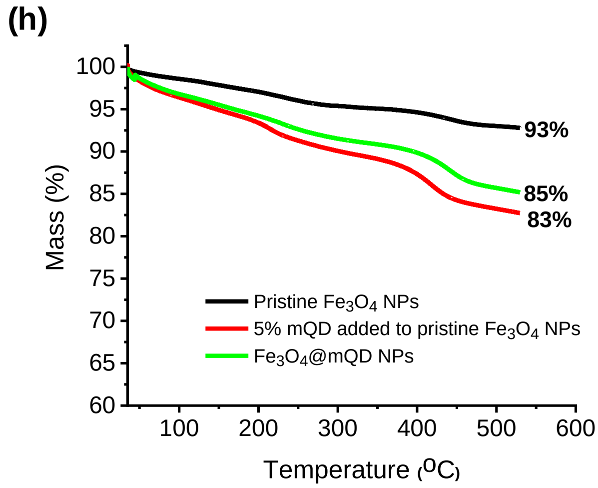


Fig. 2. (a) XRD pattern (b) nitrogen adsorption-desorption isotherms (c) SEM image (d) TEM image(e) particle size distribution (f) lattice fringes with d-spacing and SAED pattern (inset) Fe_3O_4@mQD NPs (g) FTIR spectra of pristine Fe_3O_4 NPs, free mQD and Fe_3O_4@mQD NPs (h) TGA of the pristine Fe_3O_4 NPs, pristine Fe_3O_4 NPs spiked with 5% of mQD and Fe_3O_4 @mQD NPs

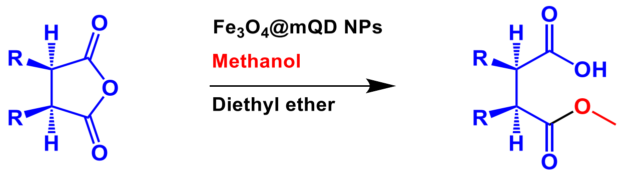
To confirm the presence of mQD on the surface of Fe_3O_4 NPs, Thermo Gravimetry Analysis (TGA) was carried out. It can be observed from the thermograms that (Fig. 2h) 7.2 % weight loss occurred at 500 °C in the case of pristine Fe_3O_4 NPs, while that of physical mixture of 5 % mQD with pristine Fe_3O_4 NPs showed 17.3 % weight loss around 500 °C. When Fe_3O_4@mQD undergoes thermal degradation, 14.8 % weight loss occurred at the same temperature range. These observations clearly indicate the chemisorption of mQD (about 6-8%) on the surface of NPs.

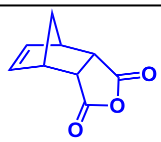
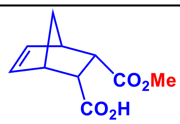
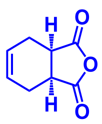
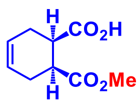
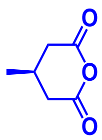
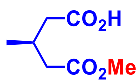
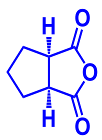
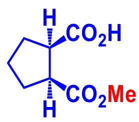
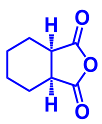
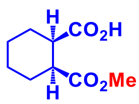
Optimization of parameters for ERO reaction

The synthesized Fe_3O_4@mQD NPs were used as chiral Lewis base catalyst for the model ERO. For the purpose, methanolysis of anhydride **1** as a model substrate was carried out in the presence of 100 mg of Fe_3O_4@mQD NPs and other reaction parameters were optimized. The amount of catalyst used for the model reaction can be considered 'catalytic quantity' as the amount of 'actual catalyst' (mQD) chemisorbed on the surface is less (6 -8 % from the TGA data). The reaction was performed by the treatment of the cyclic anhydride (1.0 mmol) with methanol (10.0 mol equiv.) for 60 h under the mentioned reaction conditions in diethylether (5.0 mL) as a solvent. The absolute configuration of the resulting chiral monoesters was determined initially by comparing their SOR ($[\alpha]_D^{25^o}$) with those reported in the literature.[21] Then the % ee of these hemiesters was determined by derivatizing it to corresponding distereomeric amide-ester (Scheme 3 in experimental section) and injecting the reaction mixture directly to HPLC system without isolation. The literature survey observed that a good % ee could be achieved when the reaction is carried out at -40 °C or lower temperature. So the model ERO of **1** was carried out at -45°C.

Screening of substrate. Anhydrides with different molecular framework were screened for the enantioselective methanolysis by setting the optimized parameters (Table 1). It can be observed from Table 1 that cis-3-methyl glutaric anhydride (**5**) undergoes methanolysis and yields hemiester with 93% ee under the optimized conditions. As discussed earlier, ERO protocol poorly collapsed when performed on succinic anhydrides in terms of % yield and selectivity. Hence, succinic anhydrides with different steric were selected for ERO. This protocol is very efficient for anhydride **1** to produce hemiester **2** with almost 98% ee and complete conversion under the optimized conditions (Table 1). The selectivity slightly deteriorated when extra steric was introduced in the ring fused with an anhydride ring. Accordingly, 99% yield with 95% ee was achieved when anhydride **7** underwent ERO by MeOH, and the same is also true when the anhydride fused ring was expanded (**9**). It was observed while performing the reaction that the total recovery of Fe_3O_4@mQD catalyst was possible by just applying the bar magnet at the bottom of the reaction flask, with the remaining reaction mixture contains only one of the enantiomers (~ 98%), which can be purified by only solvent distillation and residual drying. No additional column chromatography or recrystallization is required.

Table 1. Fe_3O_4 @mQD NPs - catalyzed ERO of different meso-cyclic anhydride.[a]



Entry	Anhydride	Products	Yield (%)[b]	ee (%)[c]
1	 **1**	 **2**	91	**98**
2	 **3**	 **4**	97	**93**
3	 **5**	 **6**	76	**93**
4	 **7**	 **8**	99	**95**
5	 **9**	 **10**	92	**96**

[a] The reaction was performed by treatment of the cyclic anhydride (1.0 mmol) with methanol (10 mmol) in the presence of Fe_3O_4 @mQD NPs (100mg) at -45°C in ether (5.0 mL). [b] Isolated yields after column chromatography. [c] Determined by HPLC analysis of the corresponding amide derivative.

Synopsis

To demonstrate the application of the as-synthesized Fe_3O_4@mQD NPs for ERO by methanolysis, we carried out the reaction in a mini pilot plant. The flow diagram of the unit processes used for the production of chiral hemiester starting from 0.1mol of anhydride **1** is shown in Fig. 3. The procedure adopted for producing the target material in a mini pilot plant is as follows:

Methanol (32 g) was added dropwise to a stirred suspension of cis-5-Norbornene-exo-2,3-dicarboxylic anhydride (16.4 g) and the Fe_3O_4 @mQD NPs (10 g) in diethyl ether (5000 ml) at -45 °C under argon. The reaction mixture was stirred at this temperature for 60 h. During this period, the anhydride gradually dissolved. After completion of the reaction the mass is transferred to another reactor enabling the separation of the catalyst. The clear solution was distilled by applying hot water of 60-65°C. After completion of the distillation the corresponding monoester 18.2g, (93% molar yield, 99% ee) was isolated from the bottom of the reactor as oil which solidified as white solid upon storage.

The recovered ether was 3600ml and 99.0% purity by GC and was having moisture less than 0.1%. It was suitable for use for next reaction without further purification.

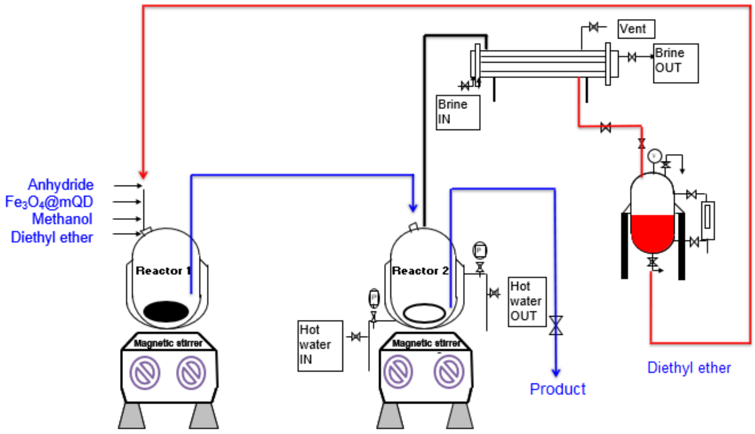
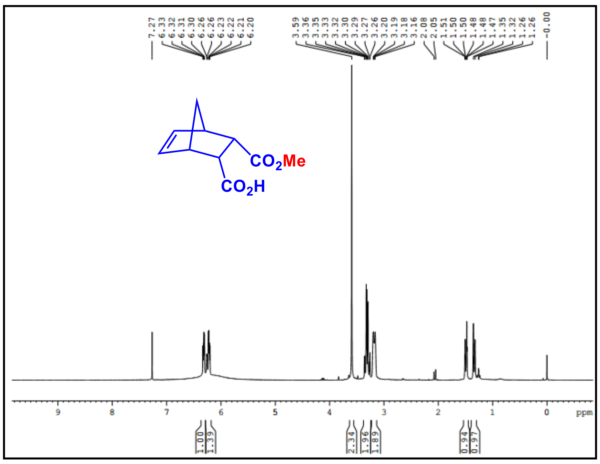
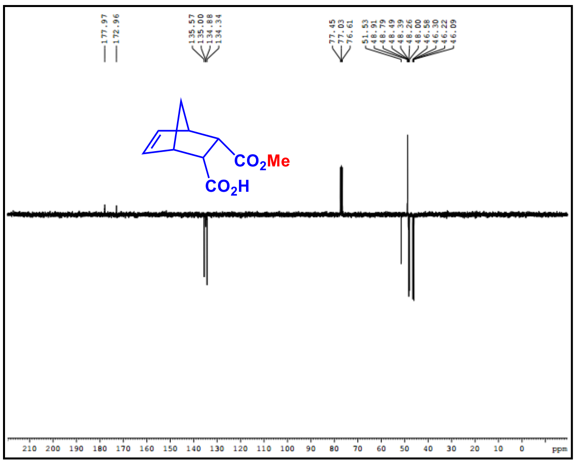


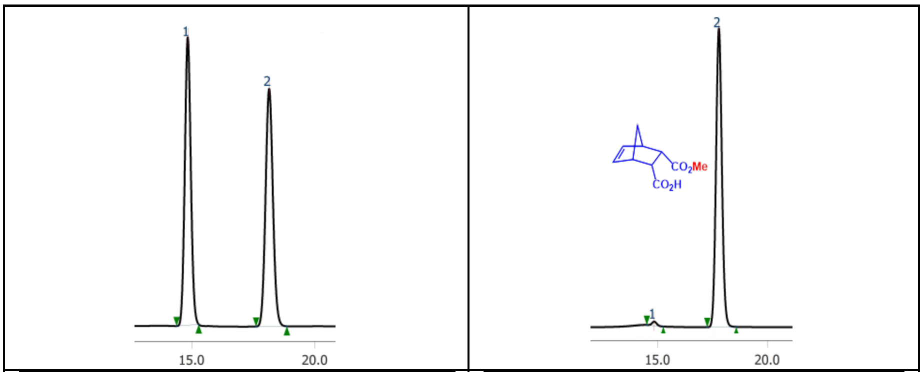
Fig. 3. Flow diagram for the pilot-scale enantioselective ring opening of *meso*-cyclic anhydrides by methanolysis in presence of Fe_3O_4@mQD NPs.

HPLC chromatograms and NMR spectra of the products and mQD intermediates:





^{1}H and ^{13}C NMR of (2*R*,3*S*)-3-*endo*-Methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid.



	Retention time	Area	Area %
1	14.837	9732165	49.816
2	18.140	9804210	50.184

	Retention time	Area	Area %
1	14.819	142127	1.125
2	18.098	12491520	98.875

HPLC chromatograms of racemic and (2*R*,3*S*)-3-*endo*-Methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid.

Conclusion

We have demonstrated that the enantioselective *meso*-cyclic anhydride ring opening by alcoholysis can be carried out in 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 ^oC in diethylether as a solvent for 60 h in the presence of catalytic amount of Fe_3O_4@mQD NPs.

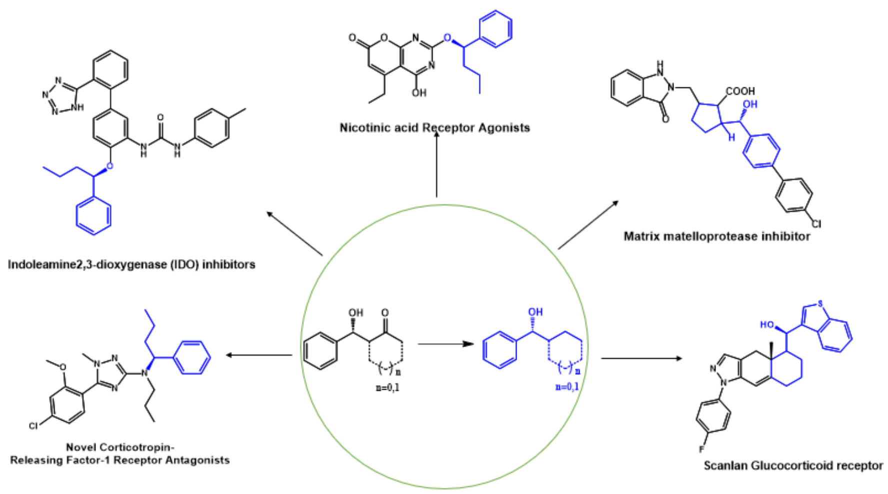
Chapter 5

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

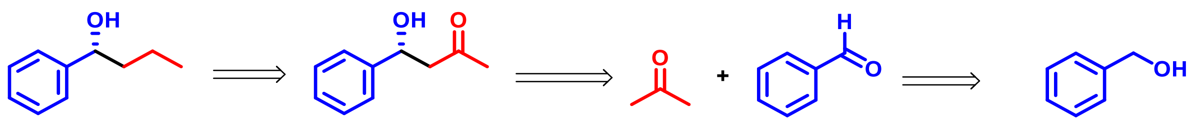
Introduction

Chiral alcohols are useful building blocks for the synthesis of many pharma products. Reduction of prochiral ketones in asymmetric fashion is the most common method to produce these chiral alcohols. Chiral alpha propyl benzyl alcohols, which are prepared by asymmetric reduction of the prochiral ketone are major components of cosmetics, fragrances and pharma products.

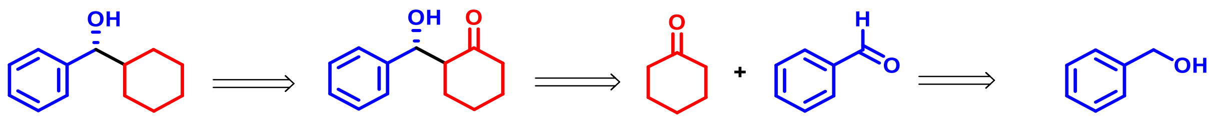
Synopsis



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.

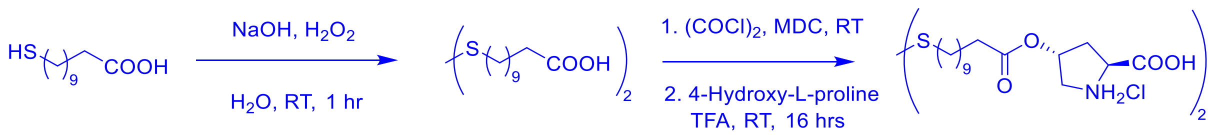


And



Preparation of catalyst:

Preparation of *disulfide derivative of proline* (the process was followed as per published process by P.L. Soti et al. in Tetrahedron 72, (2016), 1984)



11,110 -Dithiobis(undecanoic acid)

To a suspension of 11-mercaptoundecanoic acid (2.30 g, 10.00 mmol) in water (1080 mL) was added sodium hydroxide (5.60 g, 135.8 mmol) and hydrogen peroxide solution (about 30 wt %, 22 mL) was filled to a well-stirred clear solution. After being stirred for 90 min, concentrated HCl (about 30 wt %, 22 mL) was added and the mixture was extracted with EtOAc (3x300 mL). The organic solution was washed with distilled water (2x100 mL), saturated aqueous NaCl (100 mL) and dried over Na_2SO_4. After removing the solvent, disulfide compound was obtained as a white solid (1620 mg, 75%).

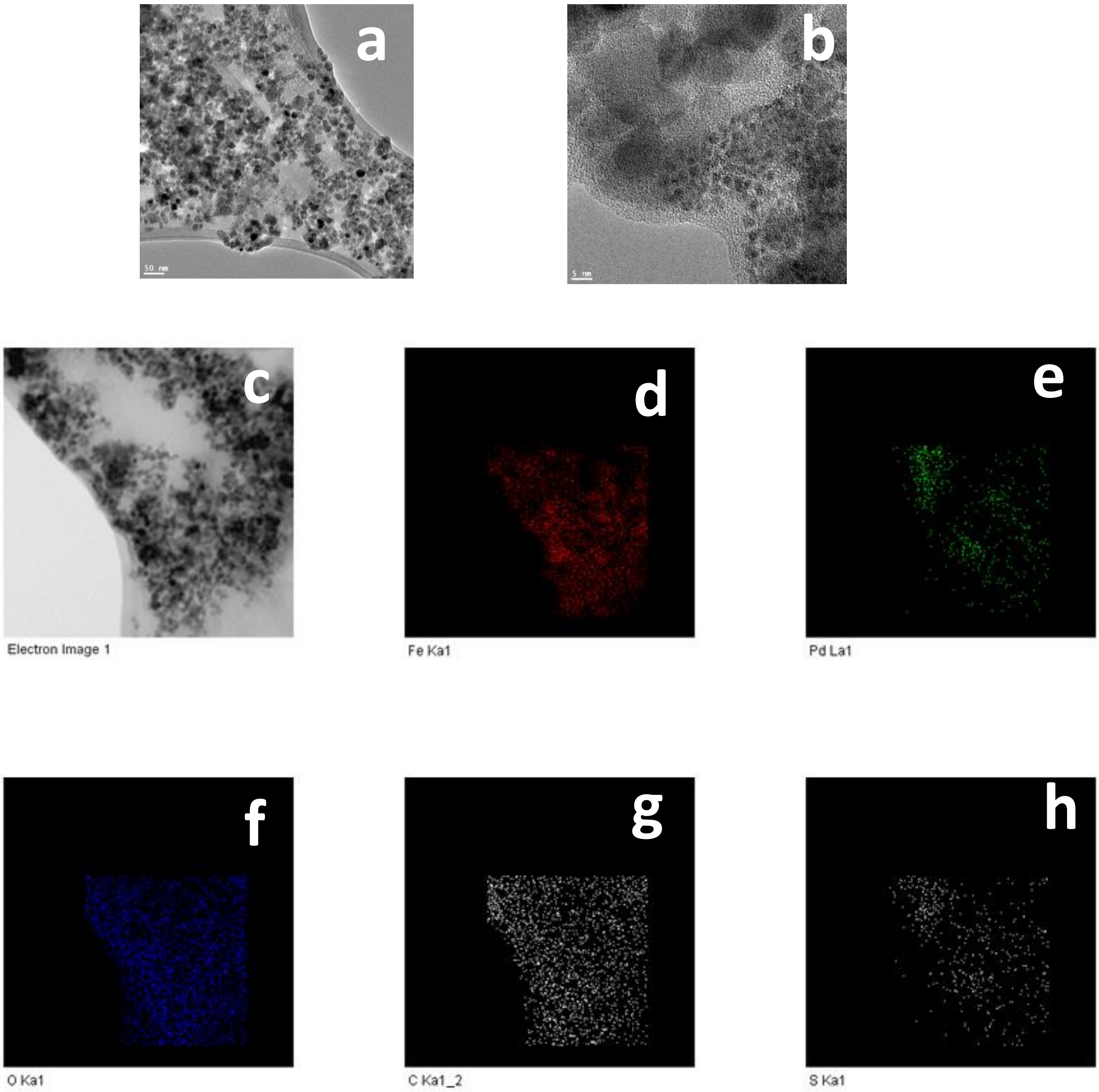
(2S,20 S,4R,40 R)-4,40 -((11,110 -Disulfanediylbis(undecanoyl))bis(oxy))bis(2-carboxypyrrolidin-1-ium) chloride (disulfide derivative of proline)

The disulfide (600 mg, 1.38 mmol) was suspended in dichloromethane (6.2 mL) in argon atmosphere and oxalyl chloride (0.4 mL, 4.88 mmol) was added dropwise to a well-stirred reaction mixture at room temperature and continued for 30 minutes. A resulted clear solution was evaporated by vacuum pump after 3 h reaction time, keeping in argon atmosphere. trans-4-hydroxy-L-proline (362 mg, 2.76 mmol) was dissolved in TFA (6.2 mL) by stirring at room temperature in argon atmosphere. The solution was cooled to about 10^{o}C with an ice bath and it was added by a dropper in one portion to acid chloride solution. The reaction mixture was stirred at room temperature for 24 h. Under cooling with an ice/water bath, Et_2O (40 mL) was added carefully to give sticky solid which was decanted, washed with Et_2O (620 mL) and dried in vacuum for 48 h to give *disulfide derivative of proline* as a cream coloured solid (806 mg, 79%).

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).

Characterization of the Catalyst

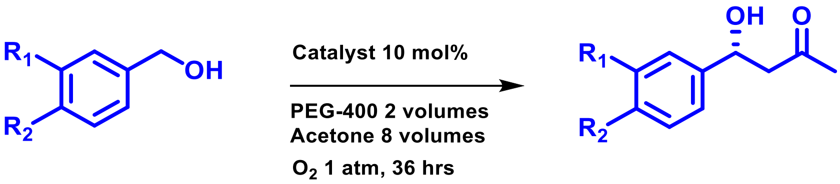


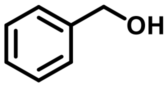
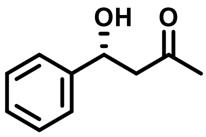
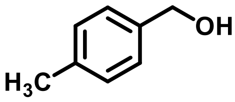
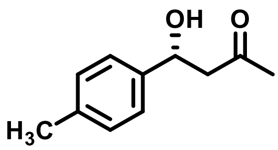
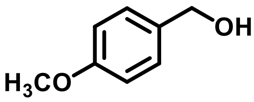
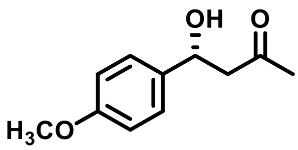
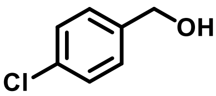
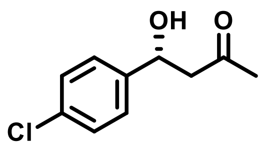
(a) And (c) TEM image (b) TEM at higher magnification. Elemental distribution analysis of mPr@Pd@Fe_3O_4 NCs, elemental mapping of (d) Fe (red), (e) Pd (green)(f) O (blue), (g) C (white) and (h) S (white).

General procedure for the synthesis of b-hydroxy ketones

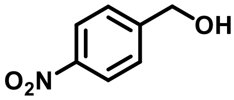
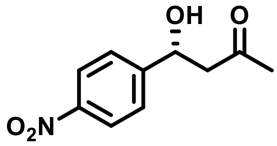
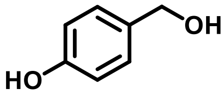
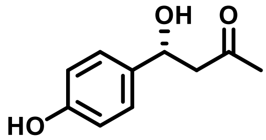
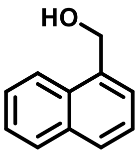
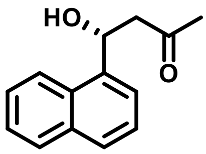
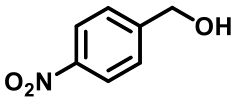
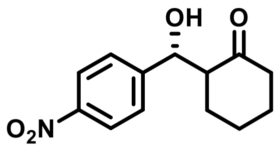
To the solution of substituted benzyl alcohol (10 mmol) in PEG-400 (2ml) was added **mPr@Pd@Fe_3O_4 catalyst** (150mg) and the resulting mixture was stirred at 40^{o}C under about 1 atmospheric pressure of oxygen till reaction complies on TLC or no starting material is left. Reaction mixture is then cooled to room temperature and acetone 8 ml is added to the reaction mixture. The reaction mass was stirred at 40^{o}C till reaction complies on TLC or no aldehyde is left. The reaction mixture was added to saturated ammonium chloride solution, the layers were separated and aqueous layer was extracted with ethyl acetate (3x25 ml) and combined organic layers were dried over anhydrous Na_2SO_4. The magnetic catalyst adhered to the magnet and was kept aside for further use. Ethyl acetate was distilled off and the residue was purified by column chromatography using ethyl acetate and hexane (1:2) as eluents.

mPr@Pd@Fe_3O_4 catalyzed, oxidation of various substituted benzyl alcohols and further asymmetric aldol condensation

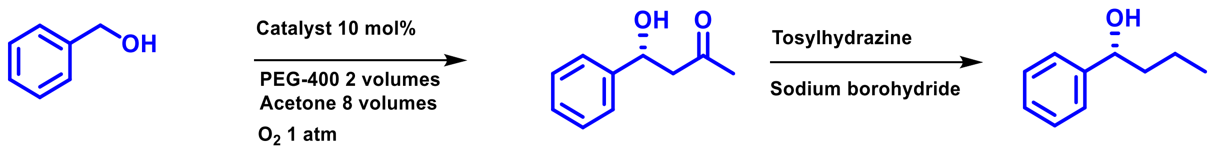


Entry	Alcohol	Aldol	Yield (%)[a]	ee (%)
1			84	Under analysis
2			78	Under analysis
3			35	Under analysis
4			84	Under analysis

Synopsis

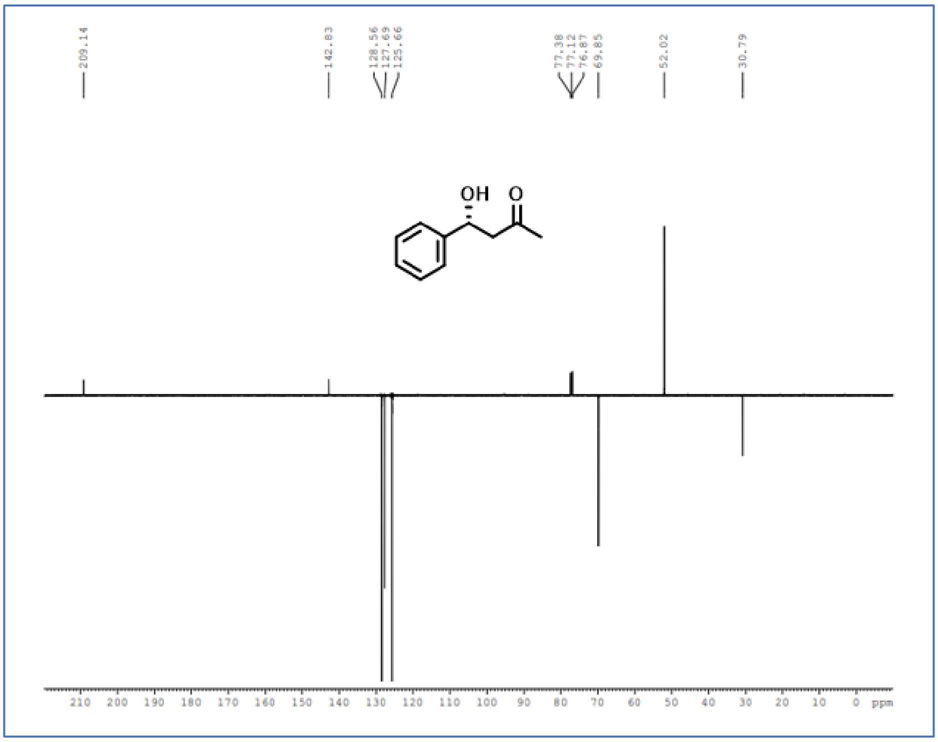
Entry	Alcohol	Aldol	Yield (%)[a]	ee (%)
5			22	Under analysis
6			-	-
7			94	Under analysis
8			35	Under analysis

Preparation of (1R)-1-phenylbutan-1-ol



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°C till reaction complies on TLC or no aldehyde is left. Acetone was removed under vacuum. To the reaction mass was added Tosyl hydrazide 2.8g and heated to 60°C for 10hrs. Further the reaction mass was cooled to room temperature and Sodium borohydride 7.56g was added lot wise in 30 mins. The reaction was further heated at 80°C for 10hrs. The reaction mixture was treated with saturated ammonium chloride solution, the layers were separated and aqueous layer was extracted with ethyl acetate (3x10 ml) and combined organic layers were dried over anhydrous Na_2SO_4. Ethyl acetate was distilled off and the residue was purified by column chromatography using ethyl acetate and hexane (1:2) as eluents gave 950mg (63%) of **(1R)-1-phenylbutan-1-ol.** $[\alpha]_D^{20}$ = +44.06 (c 1.8, CH_2Cl_2) lit[1]: $[\alpha]_D^{20}$ = +38.5 (c 1.8, CH_2Cl_2) for 83% ee.

Characterization of one of the as synthesized compounds:



^{1}H and ^{13}C NMR of 4-Hydroxy-4-phenyl-butan-2-one

Referances:

1. G. Fenyvesi, R. H. Poladi, A. Wehner, M. Joerger and R. Miller, US Pat. 20070207939 A1 (2007) to Dupont Tate & Lyle Bio Products Company.
2. J. Otera, *Esterification Methods, Reactions and Applications*, Wiley-VCH, Weinheim, Germany, 2003.
3. B. S. Furniss, A.J. Hannaford, P. W.G. Smith and A.R. Tatchell, *Vogel's Textbook of practical organic chemistry*, Longman Scientific & Technical, England, 1989.
4. P. G. M. Wuts and T. W. Greene in *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley, 2006, p. 16 –366.
5. V. Framis, F. Camps and P. Claps, *Tetrahedron Lett.*, 2004, **45**, 5031 –5033.
6. F. Iwasaki, T. Maki, O. Onomura, W. Nakashima and Y. Matsumura, *J. Org. Chem.*, 2000, **65**, 996 – 1002.
7. C. C. Leznoff, Acc. Chem. Res., 1978, **11,** 327 -333.
8. M. Lalonde and T. H. Chan, *Synthesis*, 1985, 817-845.
9. Atodiresei, I.; Schiffers, I.; Bolm, C. Stereoselective Anhydride Openings. *Chem. Rev.* **2007**, *107*, 5683-5712.
10. Chen,Y. G.; McDaid, P.; Deng, L. Asymmetric Alcoholysis of Cyclic Anhydrides. *Chem. Rev.* **2003**, *103*, 2965-298.
11. Borrmann, R.; Palchyk, V.; Pich, A.; Rueping, M. Reversible Switching and Recycling of Adaptable Organic Microgel Catalysts (Microgelzymes) for Asymmetric Organocatalytic Desymmetrization. *ACS Catal.* **2018,** *8*, 7991−7996.
12. Ivšić, T.; Dokli, I.; Rimac, A.; Hameršak, Z. Synthesis of GABOB and GABOB Based Chiral Units Possessing Distinct Protecting Groups. *Eur. J. Org. Chem.* **2014**, 631-638.
13. Huang, X.; Broadbent, S.; Dvorak, C.; Zhao, S. -H. Pilot-Plant Preparation of 3,4-Dihydropyridin-2-one Derivatives, the Core Structures of P2X7 Receptor Antagonists. *Org. Process Res. Dev.* **2010**, *14*, 612-616.
14. Willis, M. C. Enantioselective Desymmetrisation. *J. Chem. Soc., Perkin Trans. 1*. **1999**, 1765-1784.
15. Jenkins, R.; Snyder, R. L. Introduction to X-ray Powder Diffractometry, John Wiley & Sons, NY, 1996.
16. Sing, K. S. W.; Everett, D. H.; Haul, R. A. W.; Moscou, L.; R. A. Pierotti, R. A.; Rouquerol, J.; Siemieniewska, T. Reporting Physisorption Data For Gas/Solid Systems. Pure Appl. Chem. 1985, 57, 603-619.
17. Yu, J.; Zhang, L.; Cheng B.; Su, Y. Hydrothermal Preparation and Photocatalytic Activity of Hierarchically Sponge-like Macro-/Mesoporous Titania. J. Phys. Chem. C. 2007, 111, 10582-10589.
18. Shah, E.; Soni, H. P. RSC Adv. Inducing chirality on ZnS nanoparticles for asymmetric aldol condensation reactions. 2013, 3, 17453-17461.
19. Shah, E.; Upadhyay, P.; Singh, M.; Mansuri, M. S.; Begum, R.; Sheth, N.; Soni, H. P. EDTA capped iron oxide nanoparticles magnetic micelles: drug delivery vehicle for treatment of chronic myeloid leukemia and *T*1–*T*2 dual contrast agent for magnetic resonance imaging. New J. Chem. 2016, 40, 9507-9519.
20. Kakihana, M.; Nagumo, T.; Makoto, O.; Kakihana, H. Coordination structures for uranyl carboxylate complexes in aqueous solution studied by IR and carbon-13 NMR spectra. J. Phys. Chem. 1987, 91, 6128-6136.
21. C. Bolm, I. Schiffers, C. L. Dinter and A. Gerlach, J. Org. Chem., 2000, 65, 6984 -6991.

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