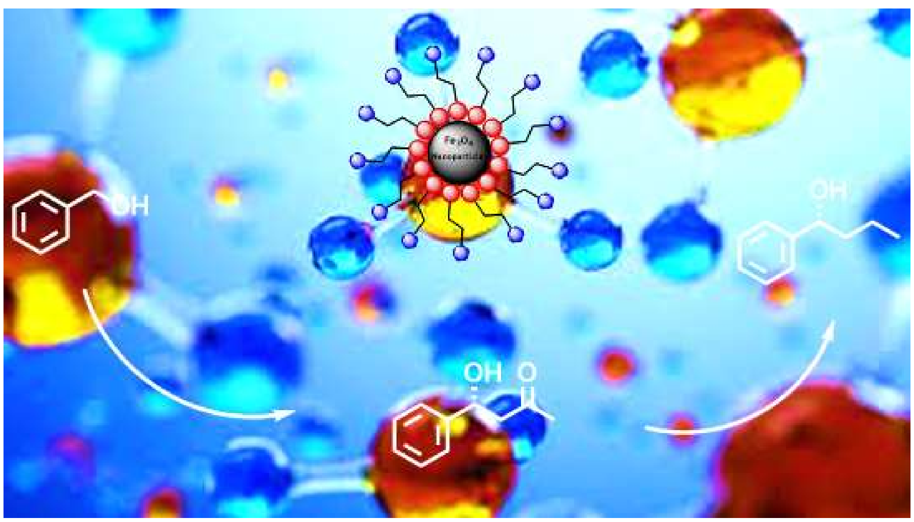
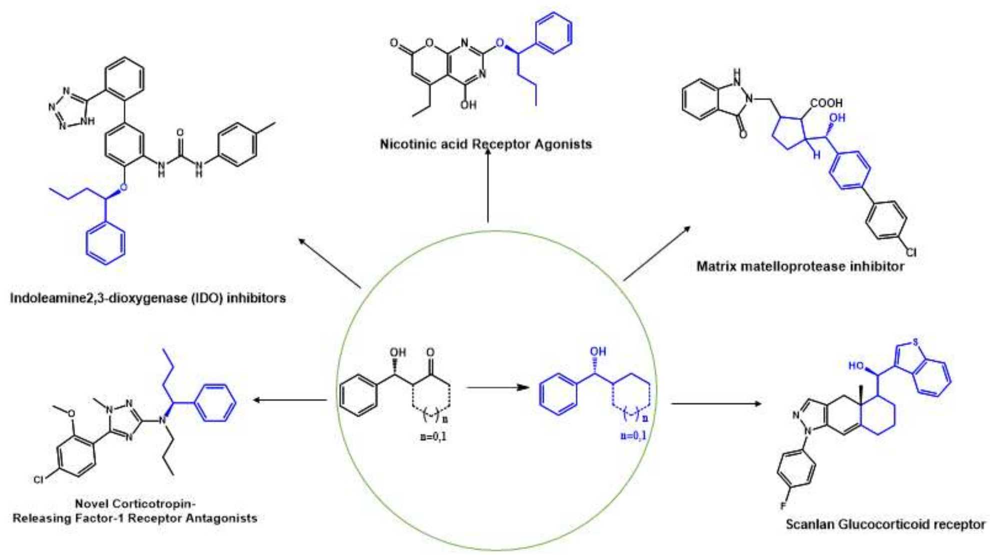
Chapter 5

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



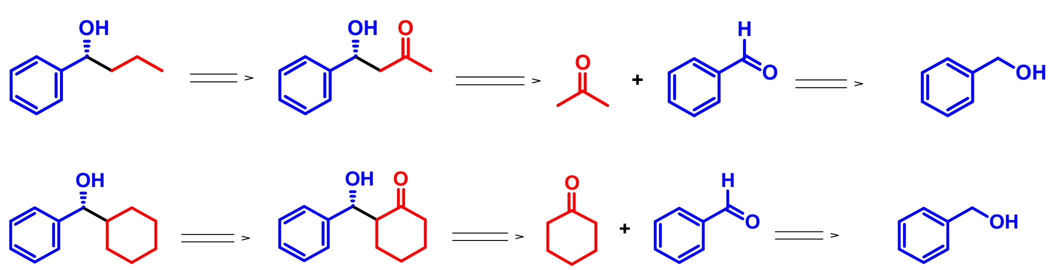
5.1. Introduction

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**.**



Scheme 1: Different active pharmaceutical ingredients having substituted chiral benzyl alcohol as an integral part

There are no reports of preparation of compound 1 or 2 directly from benzyl alcohol however it can be prepared from benzaldehyde via addition of dialkyl zinc or Grignard reagents.



Scheme 2: Retro synthetic analysis of the substituted chiral benzyl alcohols

Harada et. al.[1] reported enantioselective alkylation of aldehydes by using Grignard reagents subsequently in situ generated alkyl titanium reagents. These reactions were catalyzed by chiral titanium complex prepared from DTBP-H8-BINOL. This protocol was able to achieve chiral secondary alcohol with high enantioselectivity and yield but the reaction condition was very stringent. The reagents were extremely moisture sensitive and the temperature of -78oC was the requirement for the preparation of alkyl tin reagents. Diethyl ether is the reaction solvent which is flammable and highly volatile poses high risk at commercial scale. Soai et. al.[2] reported addition of dialkyl zinc to aldehydes catalyzed by supported ephedrine on Alumina and silica gel. The optically active secondary alcohols were obtained but with low enantioselectivity 24-59%. The reaction was carried out at 0^{o}C and for 5 days. Ishihara et. al.[3] reported enantioselective addition of Di n-alkyl zinc compounds to aldehydes and ketones catalysed by chiral phosphoramide ligands. Though the enantioselectivity and yields were high, the reaction is highly moisture sensitive and is done under nitrogen atmosphere. Diethyl ether is used as reaction solvent which is highly volatile and flammable. Due to the high molecular weight of the chiral phosphoramide ligand, it is used in very high quantity like for 5mg benzaldehyde, 22.8mg of the ligand is being used. The ligands are not recyclable. All these factors make this process not suitable for commercial scale. Takahashi et. al.[4] discussed about the enantioselective addition of alkyl titanium chiral complexes to aldehydes. The yields were low (65-80%) and enantioselectivity were poor (9.9-54%). All the reagents were of high molecular weight and were used twice the moles of the aldehyde. The reaction temperature was as below as -78^{o}C which makes this process less lucrative.

5.2. Results and discussion

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 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.

The developed mPr@Pd@Fe_3O_4 nanocomposite (NCs) (Fig.1) were characterized by TEM, elemental distribution with TEM, IR spectroscopy and surface area analysis.

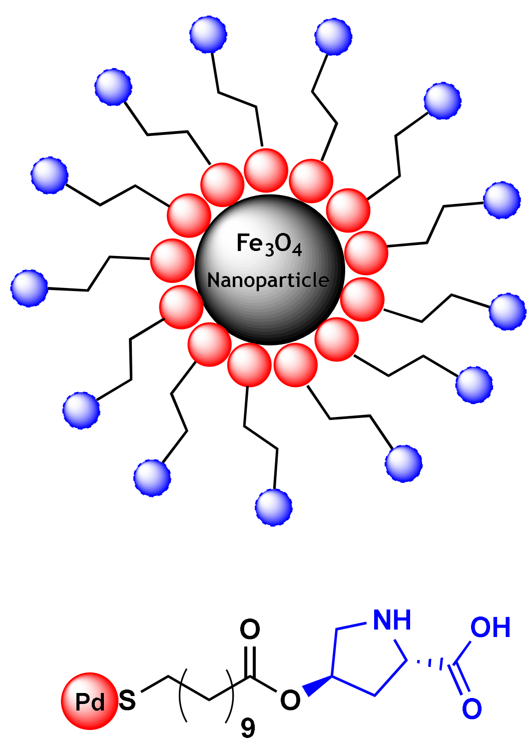


Fig. 1. Proposed structure of the prepared mPr@Pd@Fe_3O_4 nanocomposite (NCs)

5.2.1. Characterization of the Catalyst

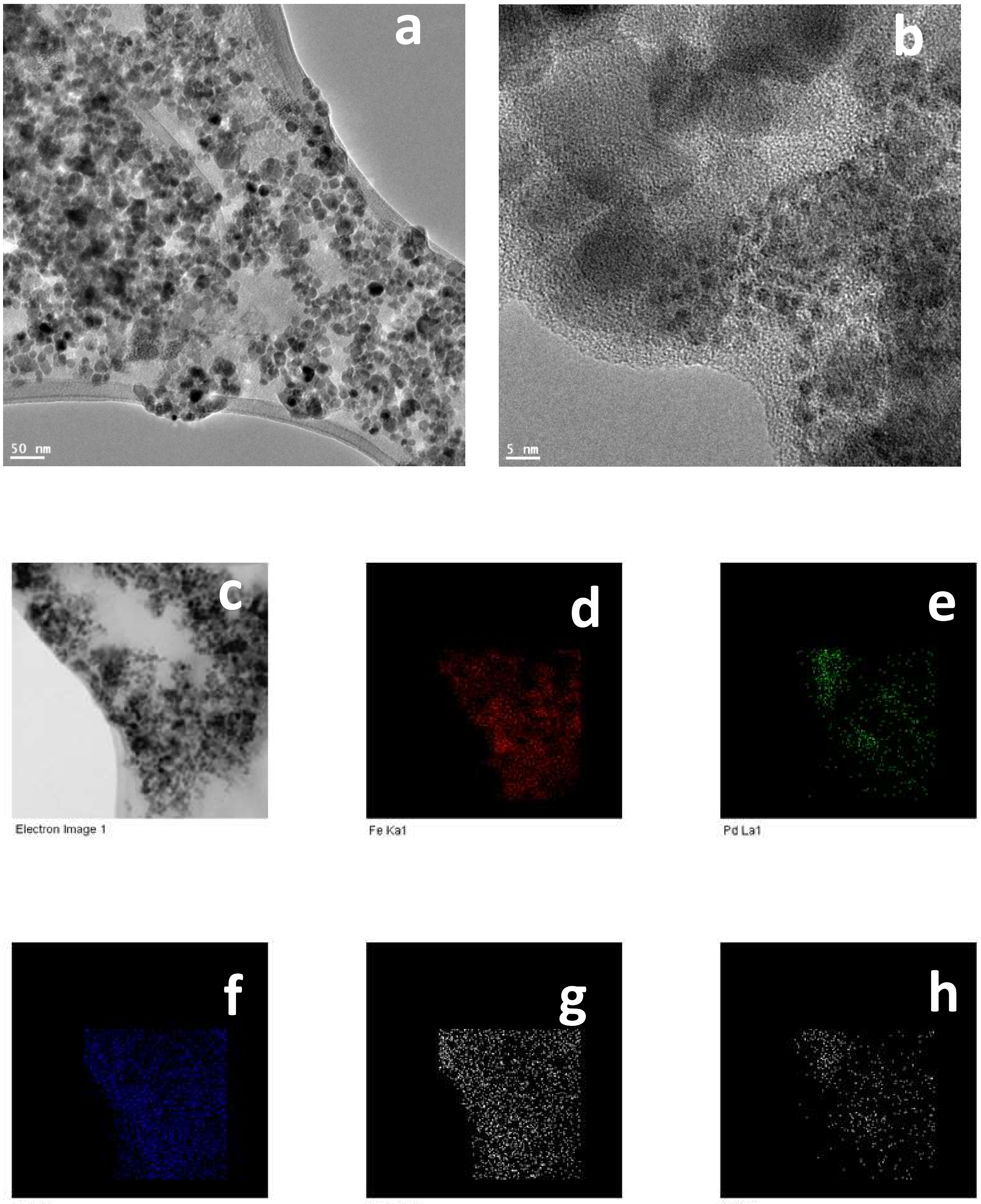


Fig. 2. (a) And (c) TEM image (b) TEM at higher magnification. Elemental distribution analysis of mPr@Pd@Fe_3O_4 NCs, elemental mapping of (d) Fe (red), (e) Pd (green)(f) O (blue), (g) C (white) and (h) S (white).

The TEM images show spherical particles and most of the particles are present in the size range of 10-50 nm. From the TEM images and Elemental distribution analysis patterns (Fig.2) it can be concluded that mPr@Pd is homogeneously distributed on the surface of host Fe_3O_4 retaining the crystallinity of the material which is necessary for the catalytic activity and recycling ability due to magnetic nature of the material.

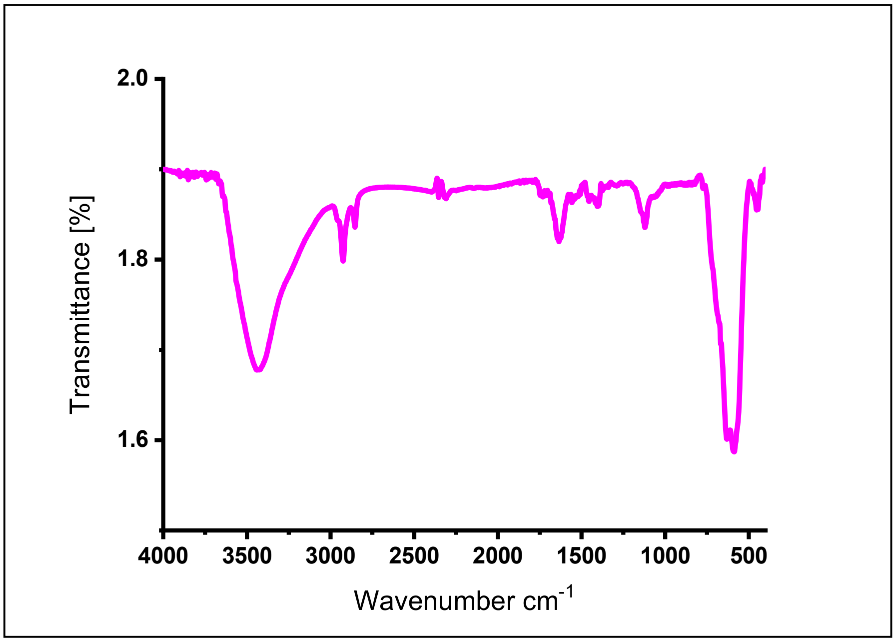


Fig. 3. IR spectra of as synthesized mPr@Pd@Fe_3O_4 NCs.

FT-IR spectroscopy is in agreement with the proposed structure of the nano composite (Fig. 3). The peaks found correspond to the C–H asymmetric, symmetric methylene stretching modes – ν_{as} (CH2) 2918 cm^{-1}, ν_s (CH2) 2856 cm^{-1}.

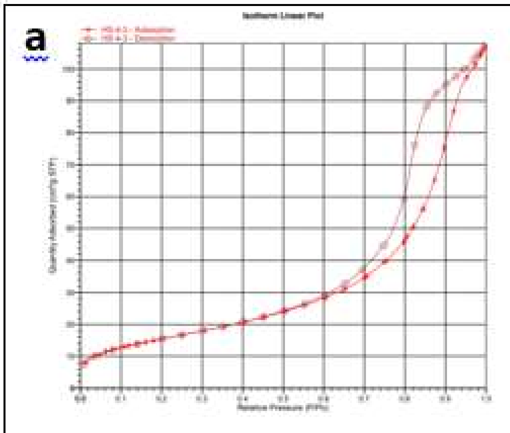
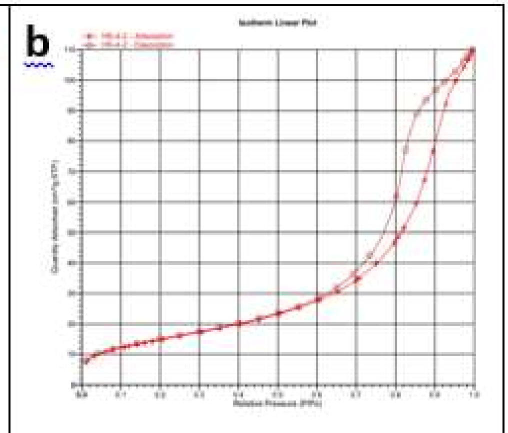
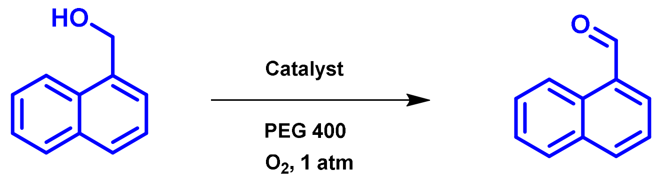
	
BET Surface Area: 56.2087 m²/g **Average Particle Size 1067.451 Å**	**BET Surface Area: 53.8621 m²/g** **Average Particle Size 1113.956 Å**

Fig. 4. BET surface area and average particle size analysis of a) Fe_3O_4 pristine nanoparticles b) mPr@Pd@Fe_3O_4 NCs.

It can be seen from the particle size of the Fe_3O_4 pristine nanoparticles was about 1067Å and after loading of the palladium and modified proline is about 1113Å. This is very marginal increase and may be due to the fact that Pd is in the form of very thin layer on the Fe_3O_4 nanoparticles. The decrease in the surface area from Fe_3O_4 pristine nanoparticles to mPr@Pd@Fe_3O_4 NCs, may be due to that the palladium has covered the entire surface of the Fe_3O_4 nanoparticles including the pores (Fig. 4).

Different catalytic system were prepared and were evaluated for the desired conversion.

Table 1. Oxidation optimization in the presence of different catalytic systems

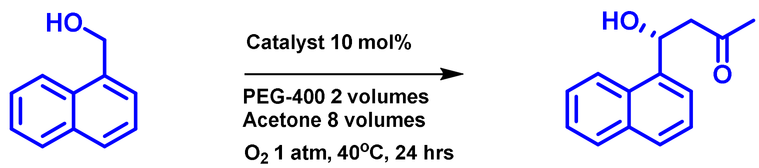


Entry	Catalyst	Time hrs	Temp. °C	alcohol conversion (%)[a]	aldehyde selectivity (%)[a]
1	Fe_3O_4 pristine NPs	48	Up to 100	-	-
2	Pd on Carbon	48	Up to 100	Less than 10	80
3	mPr@Pd NPs	24	40	89	96
4		60	25	Less than 10	-
5	mPr@Pd@Fe_3O_4 NPs	24	40	94	98
6		60	25	Less than 10	-
7	Proline@Pd@Fe_3O_4 NPs	24	40	55	92
8		60	25	Less than 10	-

[a] alcohol to aldehyde conversion and selectivity is monitored on GC.

5.2.2. Screening of the catalyst: With Fe3O4 pristine NPs and Pd on carbon the oxidation didn't proceed at all even the temperature was raised to 100°C (Table 1, Entry 1, 2). It is observed that mPr@Pd NPs, mPr@Pd@Fe_3O_4 NPs and Proline@Pd@Fe_3O_4 NPs the oxidation reaction was very slow and didn't gave a significant conversion of the product at 25°C. The conversion and selectivity of the product was best with mPr@Pd NPs and mPr@Pd@Fe_3O_4 NPs (Table 1, Entry 4, 6). But due to the best selectivity, yield and ease of separation, mPr@Pd@Fe_3O_4 NPs is considered for further development.

Table 2. **Reaction optimization in the presence of different catalytic systems**

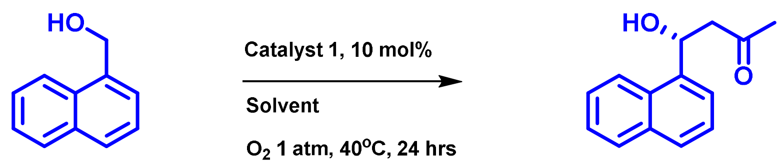


Entry	Catalyst	Yield (%)[a]	ee (%)
1	None	-	-
2	Fe_3O_4 pristine NPs	-	-
3	mPr@Pd NPs	89	98.6
4	mPr@Pd@Fe_3O_4 NPs	94	100
5	mPr	90	98.2

[a]Isolated yields after column chromatography

For oxidation and enantioselective aldol condensation, the above four catalysts were evaluated. This conversion didn't proceed in the absence of catalyst and in the presence of Fe_3O_4 pristine NPs. The reaction proceeded well in the presence of mPr@Pd NPs, mPr@Pd@Fe_3O_4 NPs and mPr. The yields were high 89-94% and high selectivity 98.2-100%. The highest yield is from the mPr@Pd@Fe_3O_4 NPs (Table 2, Entry 4), and this may be due to the easy separation of the catalyst and no loss during the work up.

Table 3. Reaction optimization in the presence of different solvent systems

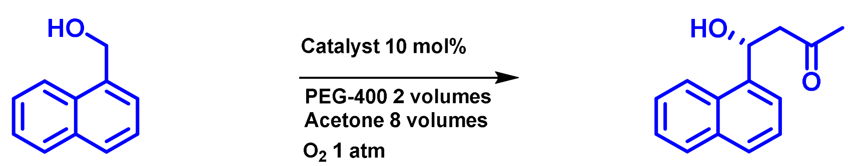


Entry	Solvent	Yield (%)[a]	ee (%)
1	Acetone	22	94.6
2	10% Acetone in $CHCl_3$	-	-
3	10% Acetone in Ethanol	-	-
4	10% Acetone in Toluene	15	96.7
5	10% Acetone in PEG 400	62	96.3
6	10% PEG 400 in Acetone	84	97.3
7	20% PEG 400 in Acetone	94	100.0
8	50% PEG 400 in Acetone	80	98.2

[a]Isolated yields after column chromatography.

5.2.3. Screening of the solvents: Different solvent systems were evaluated for this conversion and 20% PEG 400 in Acetone was the most suitable combination. The conversion and enantiomeric excess are very high up to 94%and 100% (Table 3, Entry 7).

Table 4. Effect of temperature

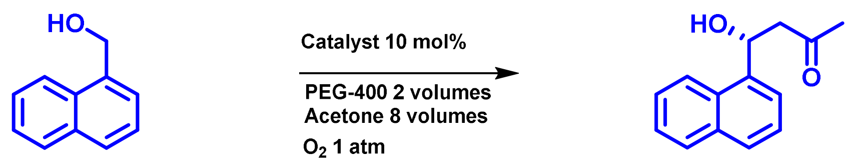


Entry	Temp (°C)	Time (h)	Yield (%)[a]	ee (%)
1	**20**	60	No product	-
2	**40**	24	94	100
3	**60**	16	90	98.4

[a]Isolated yields after column chromatography.

5.2.4. Screening of the temperature: Both the reactions, oxidation and enantioselective aldol condensation were carried with the as synthesized nano catalyst at different temperature (Table 4). At 20°C there was no oxidation product formed. At 60°C the reaction completed in 16 hrs with high isolated yield 90% and high enantiomeric excess 98.4%. The conversion and enantiomeric excess are best when the reaction temperature is maintained at 40°C, about 94% and 100%.

Table 5. Recycling of catalyst



Entry	Cycle	Yield (%)[a]	ee (%)
1	**Initial**	94	100
2	**3**	91	99.28
3	**5**	92	99.02

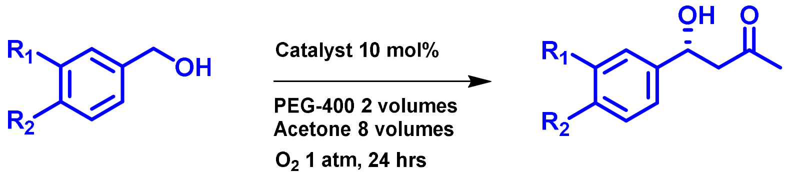
[a]Isolated yields after column chromatography.

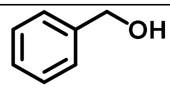
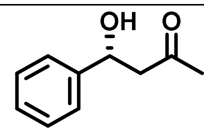
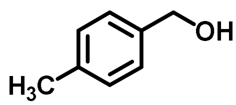
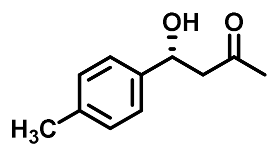
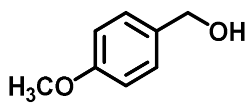
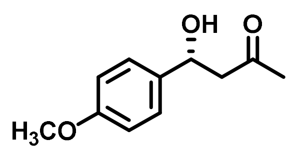
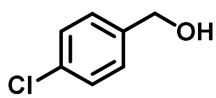
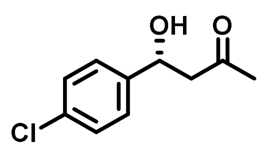
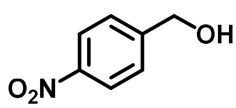
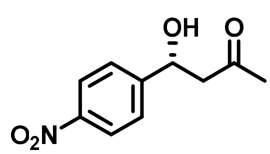
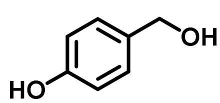
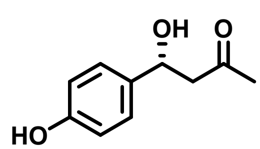
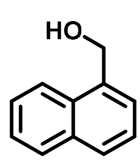
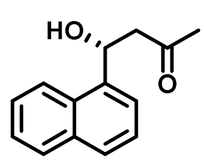
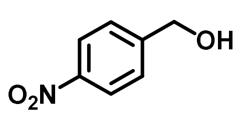
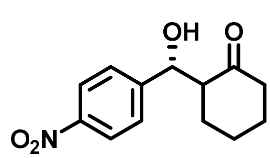
The activity of catalyst mPr@Pd@Fe_3O_4 NPs was studied up to 5 cycles and no significant drop in the yield and enantiomeric excess is observed (Table 5).

5.2.5. 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°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°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.

Table 6. mPr@Pd@Fe_3O_4 catalyzed, oxidation of various substituted benzyl alcohols and further asymmetric aldol condensation



Entry	Alcohol	Aldol	Yield (%)[a]	er (%)
1a			84	86:14
2a			78	83:17
3a			35	76:24
4a			84	91:9
5a			Less than 10	--
6a			-	--
7a			94	100:0
8a			15	dr: 87:13 er (anti): 90:10 er (syn): 96:4

[a]Isolated yields after column chromatography.

5.2.6. Screening of the Substrate: Different derivatives of benzyl alcohols were evaluated for mPr@Pd@Fe_3O_4 catalyzed oxidation and aldol condensation. It can be seen from Table 5, entry 5a, the product formation is less than 10%. This may be due to the fact that the oxidation reaction was very slow due to the electron withdrawing group –Nitro. The desired product not at all formed for the entry 6a. The oxidation reaction went well but there was no conversion of aldol product. This is due to the electron releasing group –OH. From entry 1a to 4a it can be seen that there is higher enantioselectivity of aldol product when the substitution is electron withdrawing, Cl and enantioselectivity is less when the substitution id electron releasing –OCH_3. It can also be seen from entry 8a that bulky substrate is also responsible for higher enantioselectivity.

5.3. Experimental

5.3.1. Preparation of the Catalyst

a. 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%).

b. Preparation of Fe_3O_4 pristine nanoparticles.

In brief, ferric chloride (1.42 g, 8.7 mmol) and ferrous chloride tetrahydrate (1 g, 5.02 mmol), molar ratio 1.75:1, respectively were added to 50 mL deionized water under inert atmosphere. The mixture was heated to 70 ^{o}C to obtain a clear yellow solution. The mixture was stirred vigorously with mechanical stirrer to avoid interparticle magnetic interaction. After 30 min, PVP (8 g), dissolved in (25 mL) deionized water was rapidly added. The solution was further cleared by addition of conc HCl (7 ml) and was further stirred for another 30 min. Then 20 mL ammonium hydroxide (25% in water) was rapidly added which in turn, changed the reaction color to black. The stirring was continued for 1.5 h. Finally, the black nanoparticles were separated magnetically, washed with distilled water three times 200 ml and washed with methanol three times 200 ml dried in an oven at 100 °C overnight.

Dry weight of nanoparticles: 1.2 g

c. Preparation of mPr@Pd 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, 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 as a black solid (280 mg).

d. 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).

5.3.2. 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^{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, oxygen atmosphere is removed 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. Acetone was removed under vacuum and the residue was purified with column chromatography using 30% Ethyl acetate in Hexane as eluent.

4-Hydroxy-4-phenyl-butan-2-one (1a):

Yield: 84%; ^{1}HNMR (500 MHz, CDCl3) δ (ppm) 2.19 (s, 3H), 2.78-2.92 (m, 2H), 3.47 (brs, 1H), 5.15(m, 1H), 7.27-7.36 (m, 5H) ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 30.79, 52.02, 69.85, 125.66, 127.69, 128.56, 142.83, 209.14.

Enantiomeric ratio: 86:14, determined by HPLC (Daicel Chiralpak AD-H, i-PrOH/ Hexane=2/ 98), UV 210 nm, flow rate 1.0 mL/min. *R*-isomer, *tR* 32.5 min (major) and *S*-isomer, *tR* 36.9 min (minor).

4-Hydroxy-4-(4-methylphenyl)-butan-2-one (2a):

Yield: 78%; ^{1}HNMR (500MHz, CDCl3) δ (ppm) 2.19 (s, 3H), 2.35 (s, 3H) 2.77-2.92 (m, 2H), 3.38 (s, 1H), 5.11-5.13 (d, *J*= 8.7 Hz, 2H), 7.16-7.18 (d, *J*= 7.8 Hz, 2H) 7.24-7.26 (d, *J*= 7.8 Hz, 2H), ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 21.13, 30.80, 52.03, 69.74, 125.62, 129.22, 137.38, 139.87, 209.21. Enantiomeric ratio: 83:17, determined by HPLC (Daicel Chiralpak, AD-H, *i*-PrOH /Hexane=2/98), UV 210nm, flow rate 1.0 mL/min. *R*-isomer, *tR* 50.9 min (minor) and *S*-isomer, *tR* 62.4 min (major).

4-Hydroxy-4-(4-methoxyphenyl)-butan-2-one (3a):

Yield: 35%; ^{1}HNMR (500MHz, CDCl3) δ (ppm) 2.20 (s, 3H), 3.81 (s, 3H) 2.77-2.92 (m, 2H), 3.28 (s, 1H), 5.09-5.12 (m, 1H), 6.88-6.90 (d, 2H) 7.28-7.29 (d, 2H), ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 30.80, 51.97, 55.31, 69.51, 113.92, 126.94, 134.94, 159.12, 209.21; Enantiomeric ratio: 76:24, determined by HPLC (Daicel Chiralpak, AD-H, *i*-PrOH /Hexane=10/90), UV 210nm, flow rate 1.0 mL/min. *R*-isomer, *tR* 11.4 min (major) and *S*-isomer, *tR* 12.8 min (minor).

4-Hydroxy-4-(4’-chlorophenyl)-butan-2-one (4a):

Yield: 84%; 1H NMR (500 MHz, CDCl3) δ (ppm) 2.19 (s, 3H), 2.76-2.87 (m, 2H), 3.52 (brs, 1H), 5.12 (m, 1H), 7.28-7.33 (m,4H). 13C NMR (125 MHz, CDCl3) δ (ppm) 30.78, 51.83, 69.15, 127.06, 128.67, 133.30, 141.27, 208.96

Enantiomeric ratio: 91:9, determined by HPLC (Daicel Chiralpak AD-H, i-PrOH/ Hexane=2/98), UV 210 nm, flow rate 0.5 mL/min. R-isomer, tR 70.2 min (major) and S-isomer, tR 86.6 min (minor).

4-Hydroxy-4-(4’-nitrophenyl)-butan-2-one (5a):

Yield: less than 10%, ^{1}H NMR (500 MHz, CDCl3) δ (ppm) 2.22 (s, 3H), 2.86 (m, 2H), 3.72 (d, *J*= 3.2 Hz, 1H), 5.27 (m, 1H), 7.54 (d, *J*= 7.0 Hz, 2H), 8.20 (d, *J*= 7.0 Hz, 2H). ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 30.73, 51.53, 68.90, 123.76, 126.45, 147.29, 150.08, 208.55.

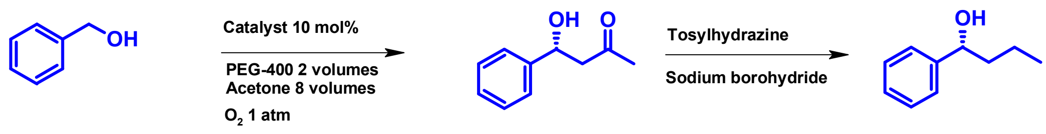
4-(1-Naphthyl)-4-hydroxy-2-butanone (7a):

Yield: 94%; ^{1}HNMR (500MHz, CDCl3) δ (ppm) 2.21 (s, 3H), 2.94-3.02 (m, 2H), 3.42 (brs, 1H), 5. 93-5.96 (t, 1H), 7.46-7.53 (m, 3H), 7.68 (d, *J*= 10.2 Hz, 1H), 7.78 (d, *J*= 11.4 Hz, 1H), 7.87 (m, 1H), 8.00 (m, 1H), ^{13}C NMR (125 MHz, CDCl3) δ (ppm) 30.81, 51.35, 66.70, 122.75, 123.01, 125.58, 125.60, 126.25, 128.13, 129.06, 129.88, 133.78, 138.24, 207.27. Enantiomeric ratio: 99.85:0.15, determined by HPLC (Daicel Chiralpak AD-H, i-PrOH/ Hexane=2/98), UV 210nm, flow rate 1.0 mL/min. *R*-isomer, *tR* 68.4 min (minor) and *S*-isomer, *tR* 79.4 min (major)

2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone (8a):

yield: 15%; *Diastereomeric ratio*= 87:13; ^{1}H NMR (500 MHz, CDCl3) δ (ppm) 1.55-2.15 (m, 6H), 2.38-2.50 (m, 2H), 2.52-2.62 (m, 1H), 4.09 (d, *J*= 1.3Hz, 1H), 4.91 (d, *J*= 8.6 Hz, *J*= 2.8 Hz, 1H), 7.52 (d, *J*=3 .9 Hz, 2H), 8.23 (d, *J*= 3.9 Hz, 2H). Enantiomeric ratio (anti): 90:10, enantiomeric ratio (syn): 96:4, determined by HPLC (Daicel Chiralpak AD-H, i-PrOH/ Hexane=20/80), UV 210 nm, flow rate 0.5 mL/min. For syn *tR* (major) 10.5 min, *tR* (minor) min. For anti *tR* (major) 14.4 min, *tR* (minor) 11.4min.

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



Scheme 3: One pot synthesis of (1R)-1-phenylbutan-1-ol from benzyl alcohol

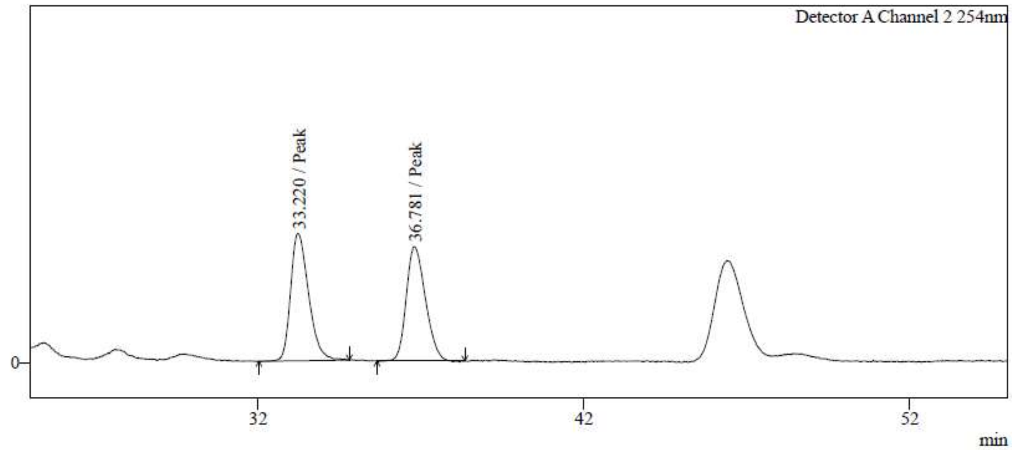
To the solution of benzyl alcohol 1.08g (10 mmol) in PEG-400 (2ml) was added mPr@Pd@Fe_3O_4 catalyst (150mg) and the resulting mixture was stirred at 40^{o}C under about 1 atmospheric pressure of oxygen till reaction complies on TLC or no starting material is left. Reaction mixture is then cooled to room temperature, oxygen atmosphere is removed 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. Acetone was removed under vacuum. To the reaction mass was added Tosyl hydrazide 2.8g and heated to 60^{o}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^{o}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]: $[\alpha]_D^{20}$ = +33.5 (c 1.8, CH_2Cl_2) for 75% ee.

5.3.4. Characterization data of the synthesized compounds

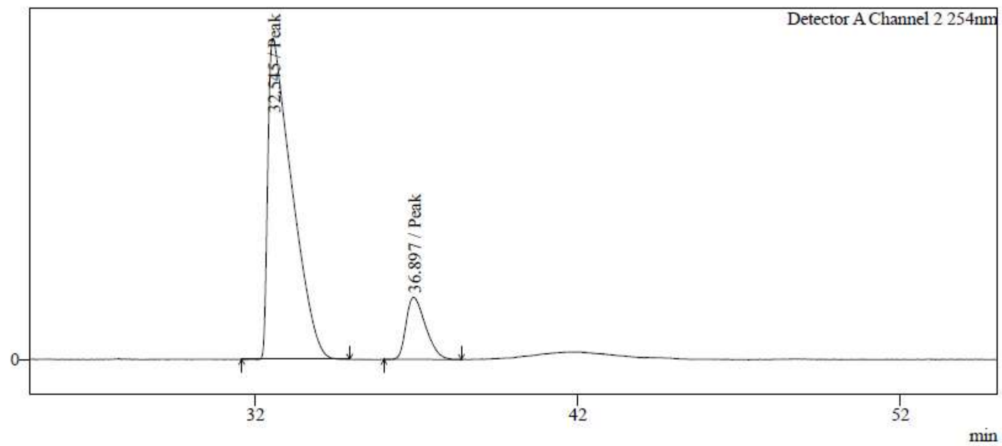
An X-ray powder diffraction (XRD) pattern was obtained using an X-ray powder diffractometer (Philips X'pert MPD system) with Cu Kα radiation, λ = 0.15418 nm. Particle size with elemental mapping was carried out by TEM (JEOL-JEM-2100) at 200 kV. FT-IR spectra of all compounds were recorded with Bruker FTIR spectrometer using KBr pallets in the range of 400 to 4000 cm^{-1}. Optical rotations were measured on JACSO P-2000 polarimeter and HPLC analyses were carried out on Jasco HPLC system at 280nm.

The ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 500 and 125 MHz spectrometer using TMS as an internal standard in $CDCl_3$.

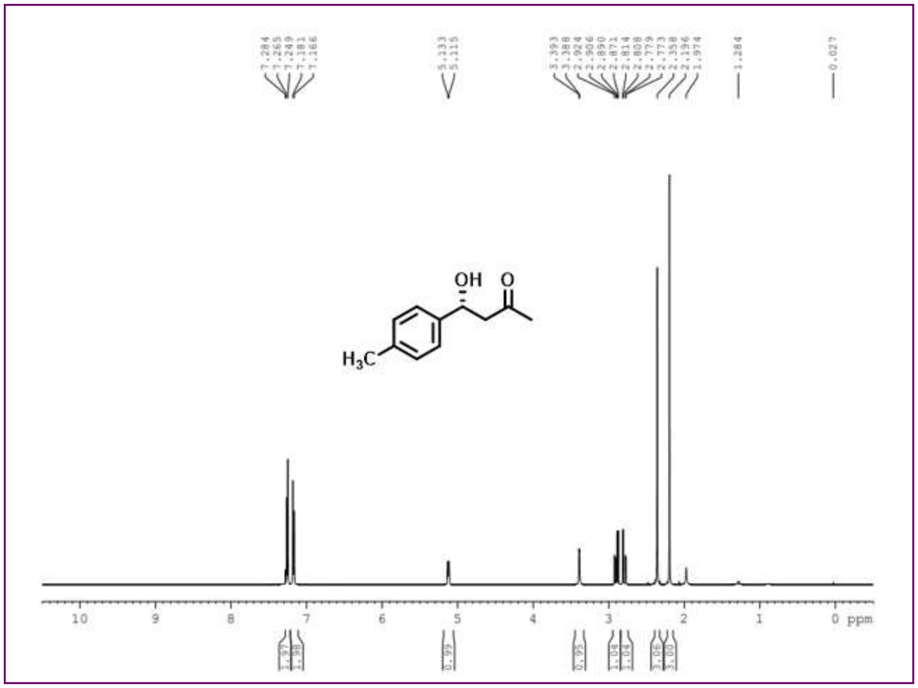
^{1}H and ^{13}C NMR of 4-Hydroxy-4-phenyl-butan-2-one

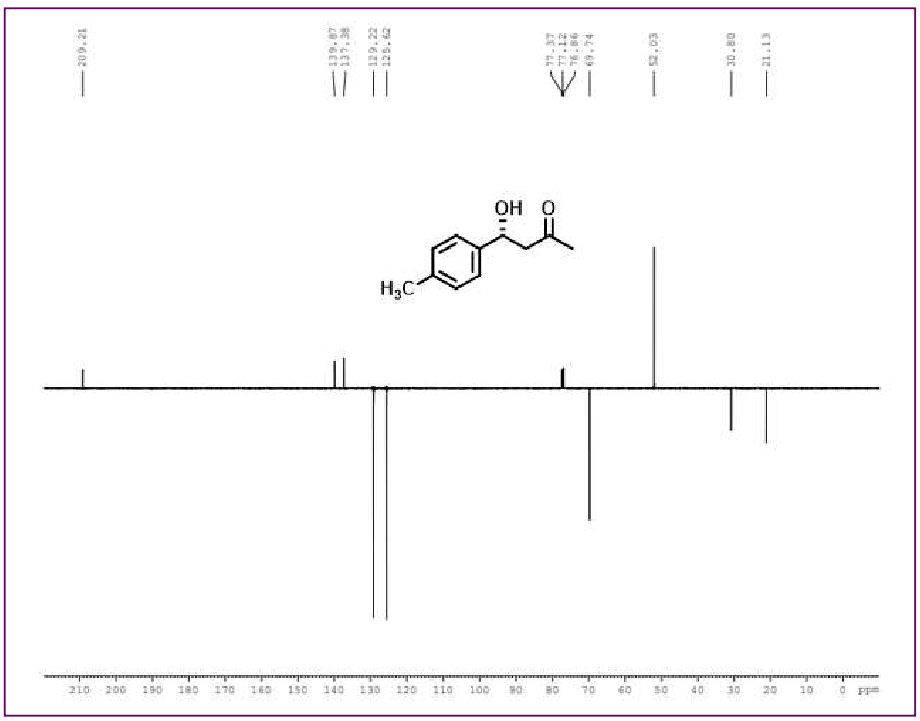


Name	RT	Area	% Area
Peak1	33.22	137757	51.249
Peak2	36.78	131044	48.751

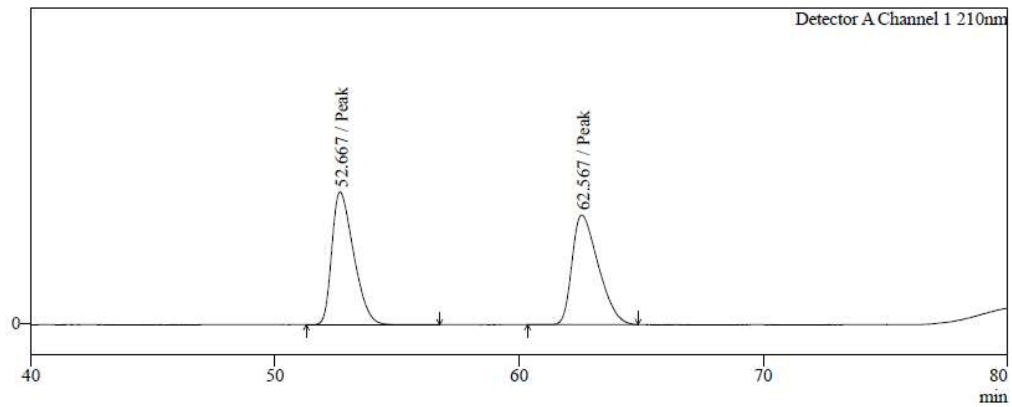


Name	RT	Area	% Area
Peak1	32.54	1421196	86.398
Peak2	36.90	223754	13.602

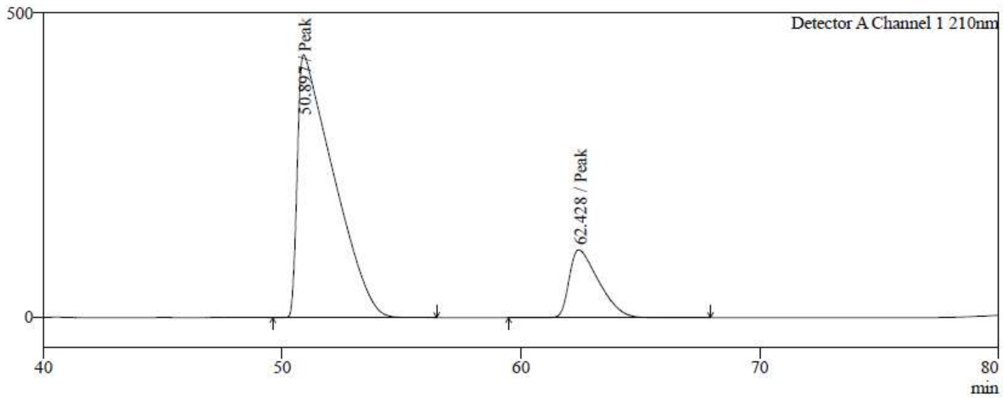




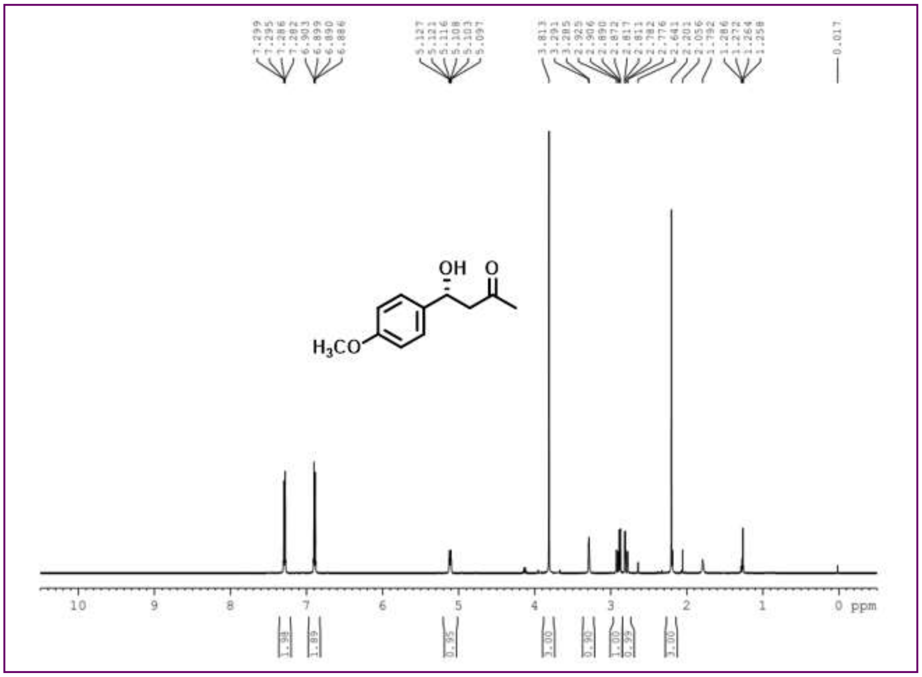
^{1}H and ^{13}C NMR of 4-Hydroxy-4-(4-methylphenyl)-butan-2-one

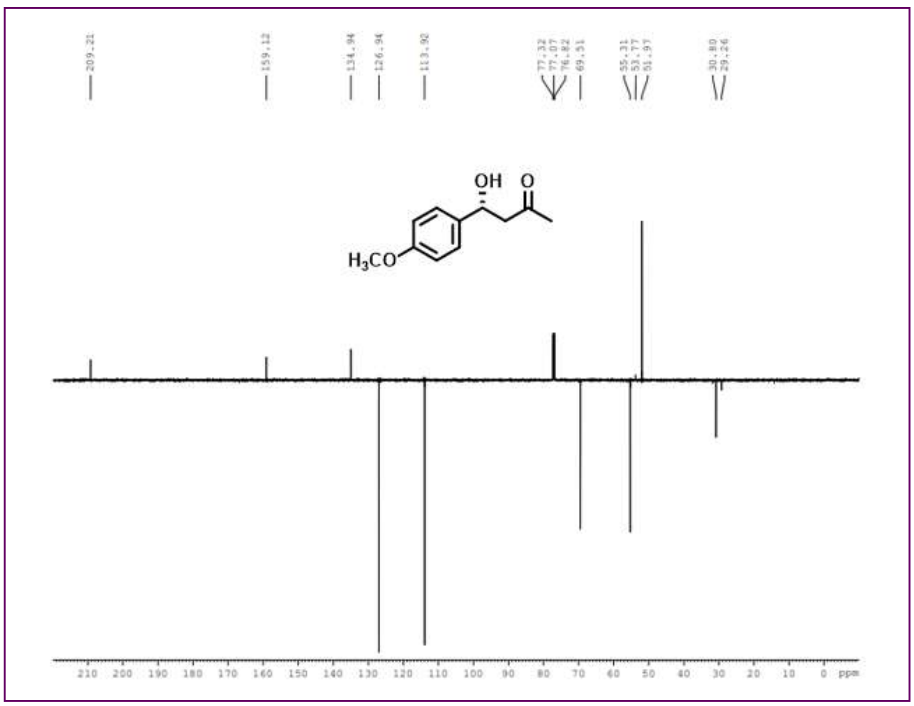


Name	RT	Area	% Area
Peak1	52.67	5229876	50.113
Peak2	62.57	5206268	49.887

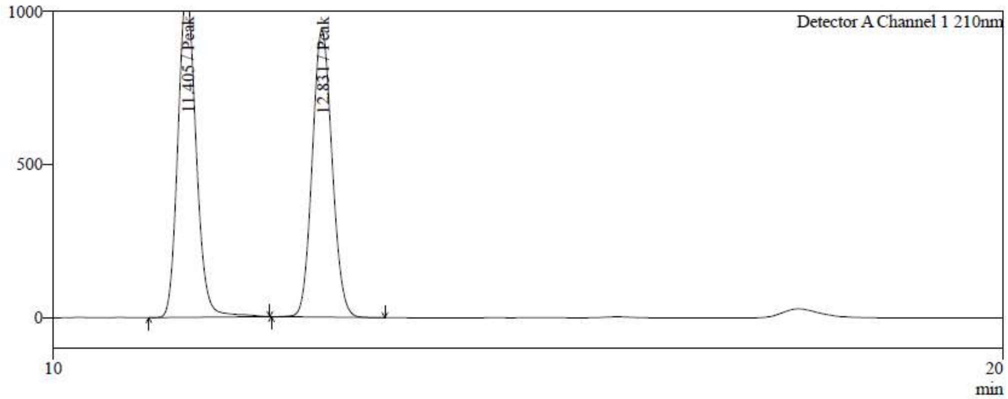


Name	RT	Area	% Area
Peak1	50.90	45329688	82.685
Peak2	62.43	9492252	17.315

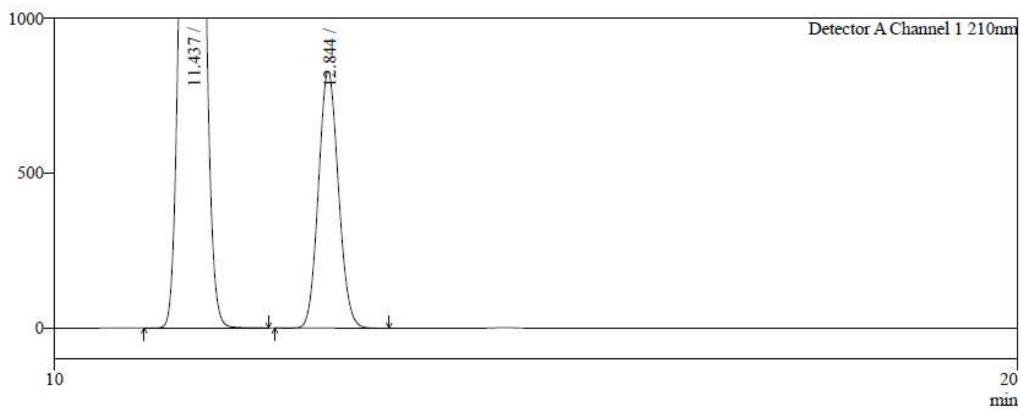




[1]H and [13]C NMR of 4-Hydroxy-4-(4-methoxyphenyl)-butan-2-one

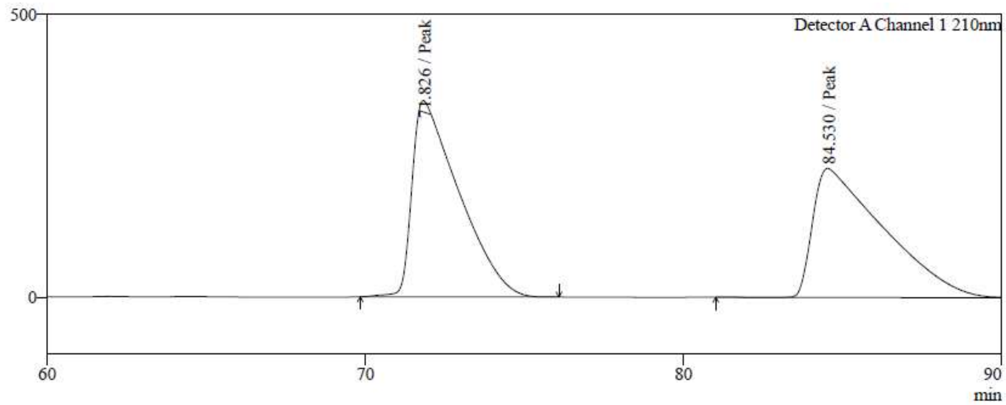


Name	RT	Area	% Area
Peak1	11.41	14132934	50.952
Peak2	12.83	13604905	49.048

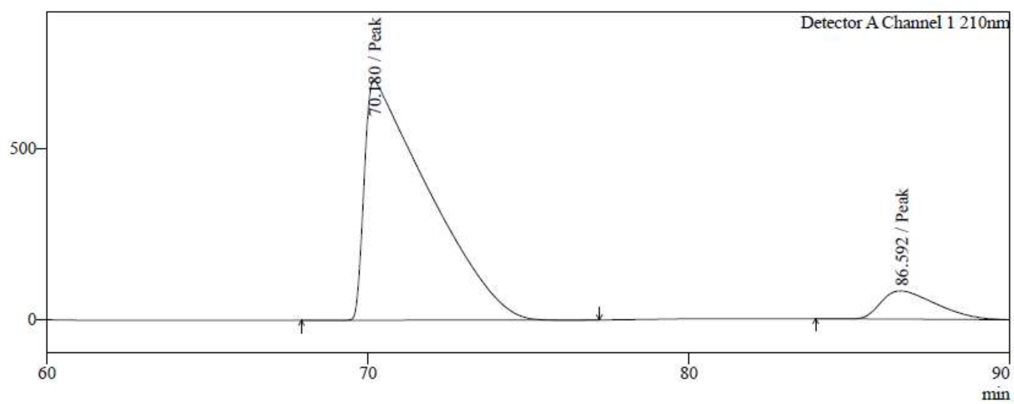


Name	RT	Area	% Area
Peak1	11.44	37303882	75.74
Peak2	12.84	11942997	24.26

^{1}H and ^{13}C NMR of 4-Hydroxy-4-(4'-chlorophenyl)-butan-2-one

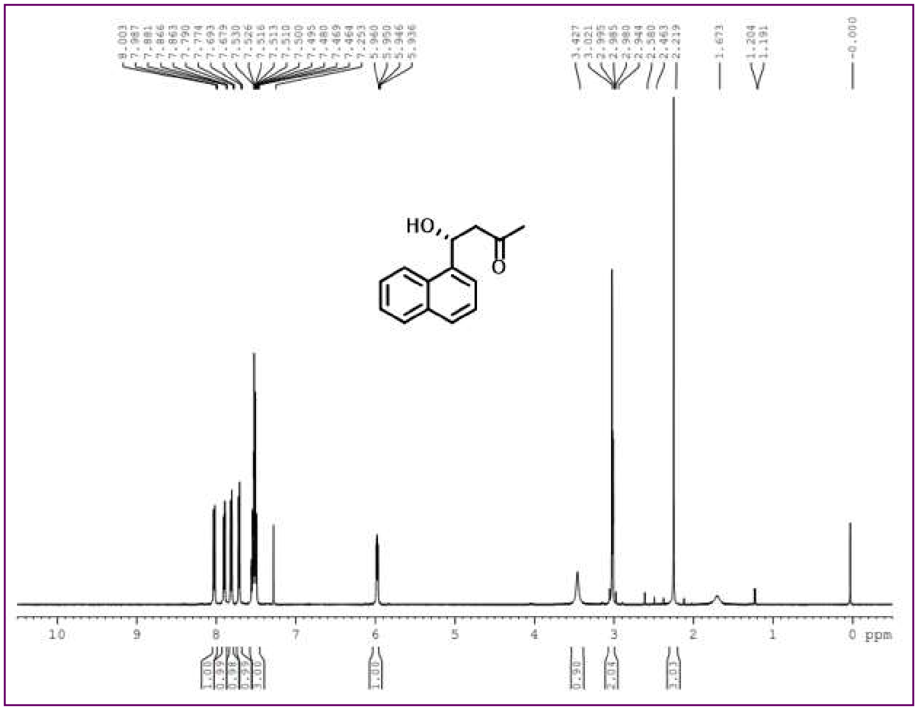


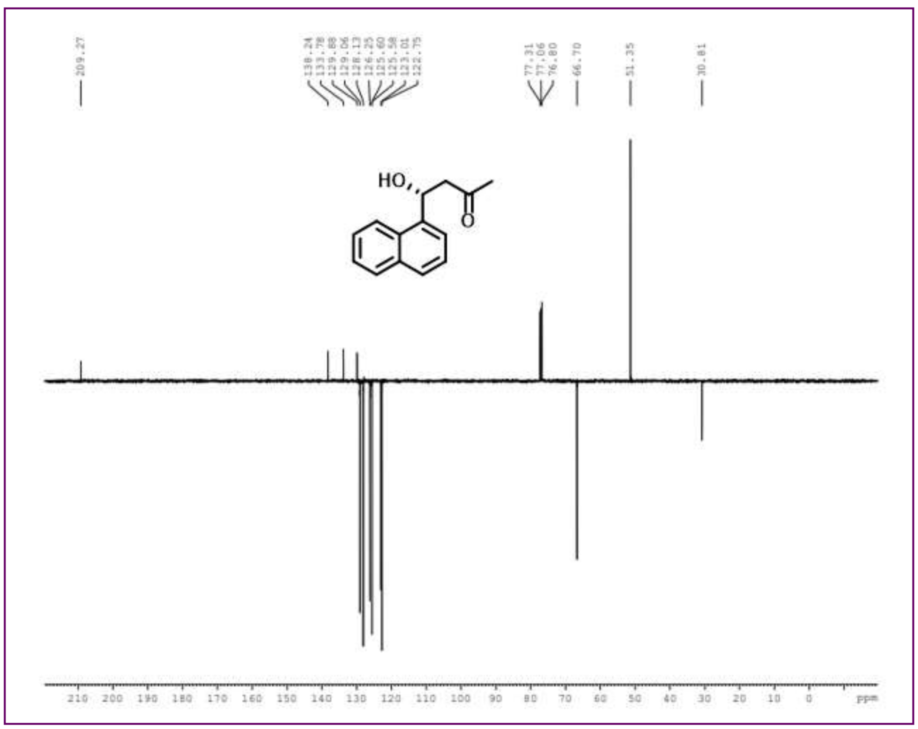
Name	RT	Area	% Area
Peak1	71.83	35579601	50.263
Peak2	84.53	35206559	49.737



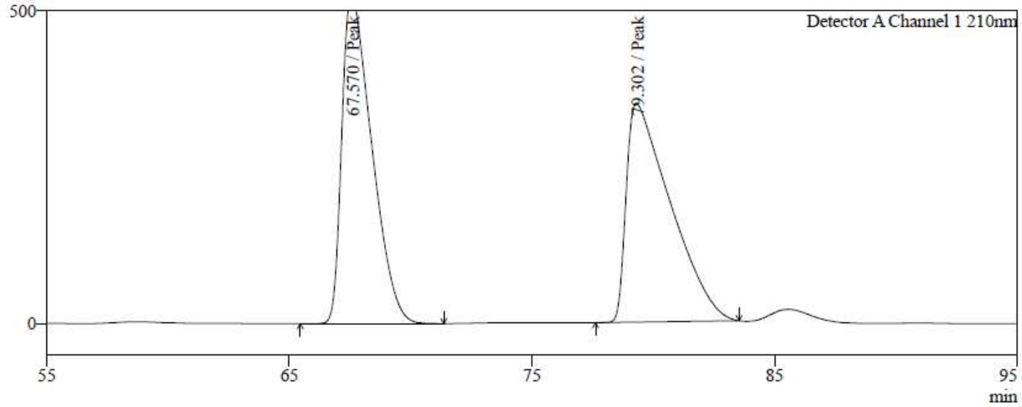
Name	RT	Area	% Area
Peak1	70.18	98211656	90.905
Peak2	86.59	9826144	9.095

^{1}H and ^{13}C NMR of 4-Hydroxy-4-(4'-nitrophenyl)-butan-2-one



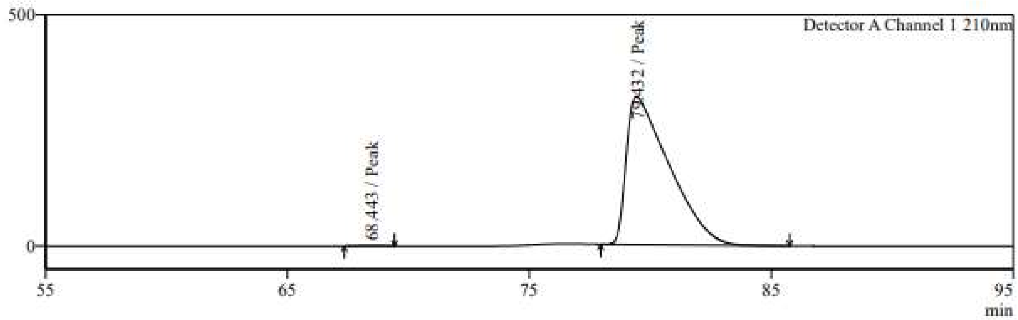


^{1}H and ^{13}C NMR of 4-(1-Naphthyl)-4-hydroxy-2-butanone

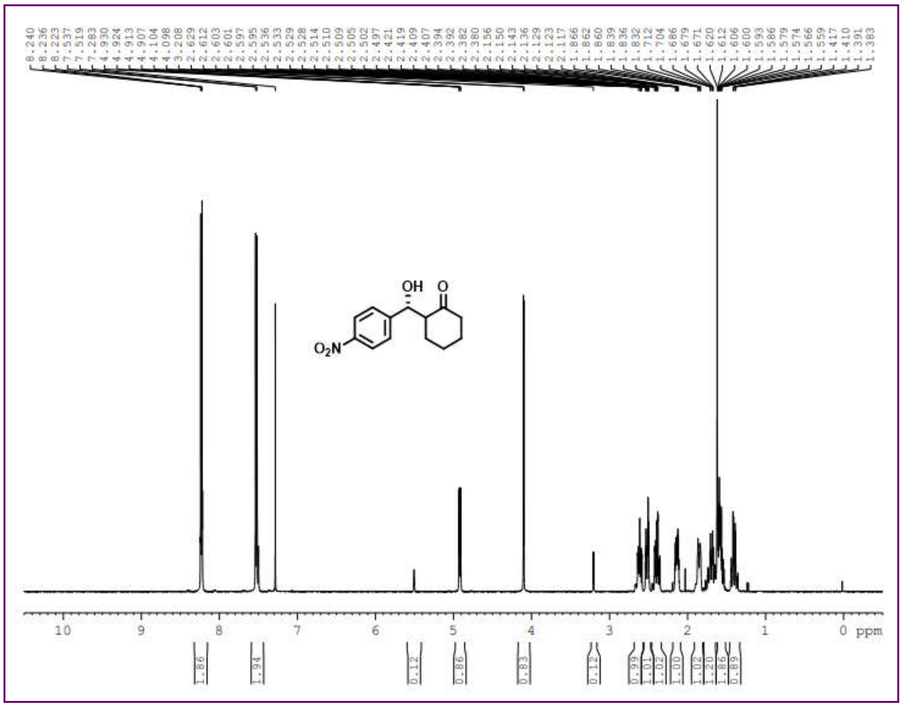


Name	RT	Area	% Area
Peak1	67.57	44943900	
Peak2	79.30	44275783	

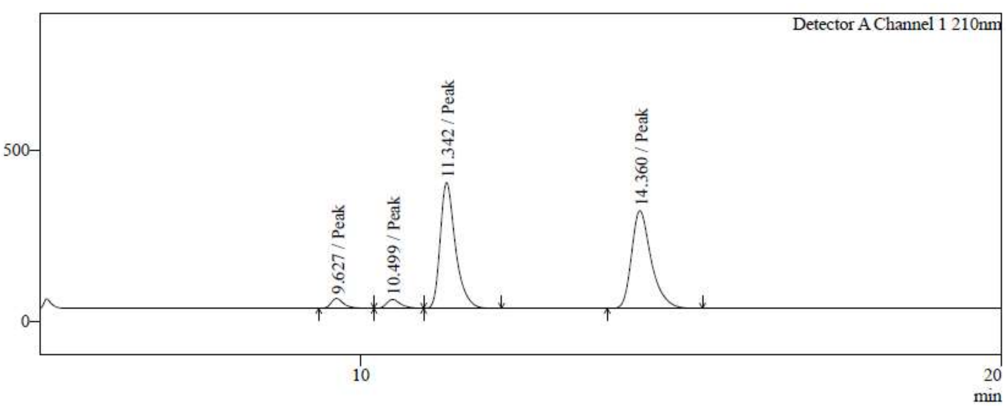
2



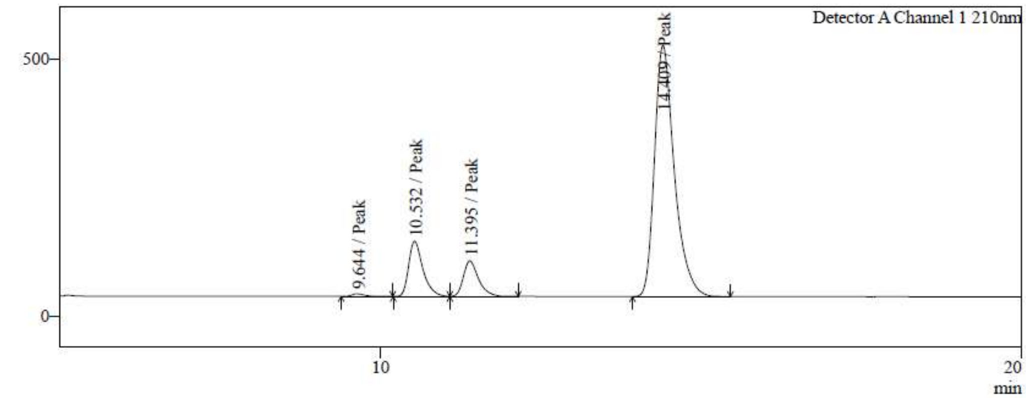
Name	RT	Area	% Area
Peak1	68.44	62019	0.15
Peak2	79.43	39596863	99.85



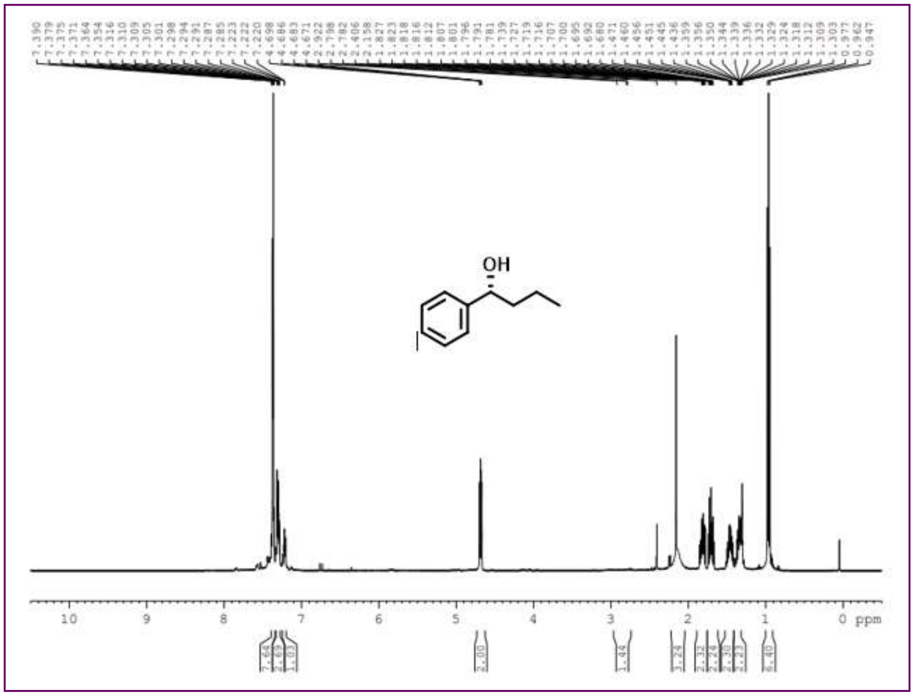
^{1}H NMR of 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone

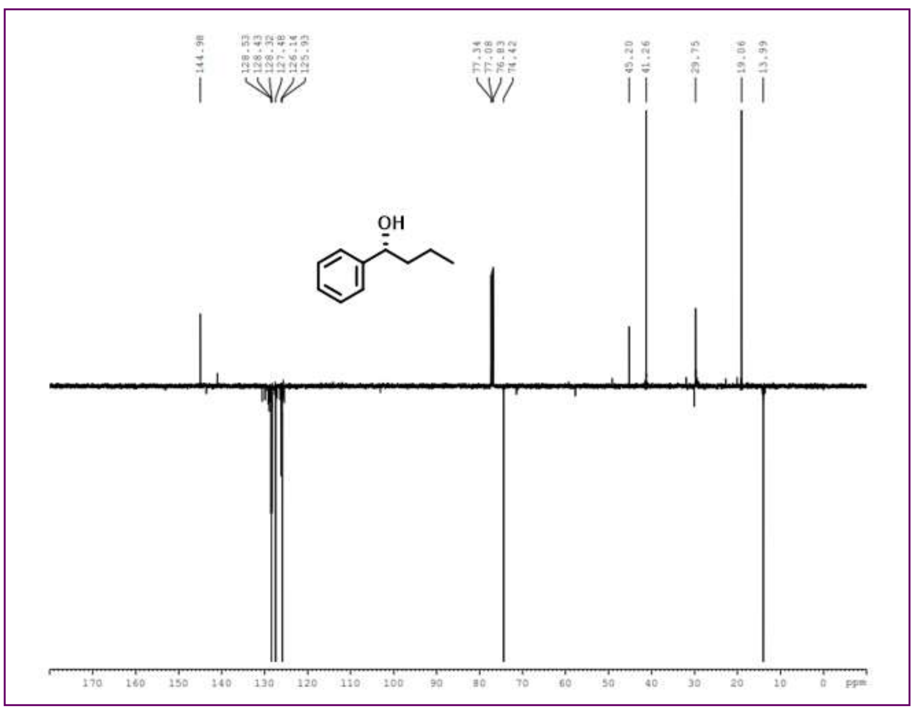


	Name	RT	Area	% Area
1	Peak1	9.63	396963	3.053
2	Peak2	10.50	392819	3.021
3	Peak3	11.34	6103523	46.942
4	Peak4	14.36	6109090	46.984



	Name	RT	Area	% Area
1	Peak1	9.64	68756	0.514
2	Peak2	10.53	1663104	12.435
3	Peak3	11.39	1139851	8.523
4	Peak4	14.41	10502304	78.528

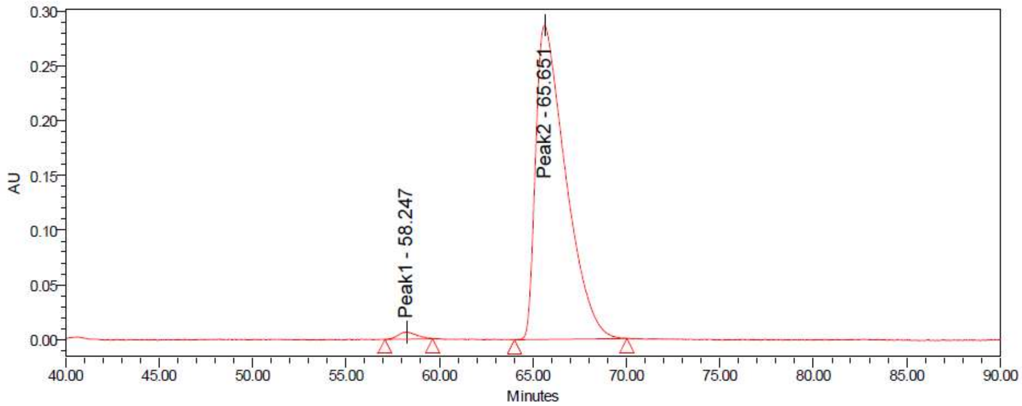




^{1}H and ^{13}C NMR of (R)-1-phenylbutan-1-ol

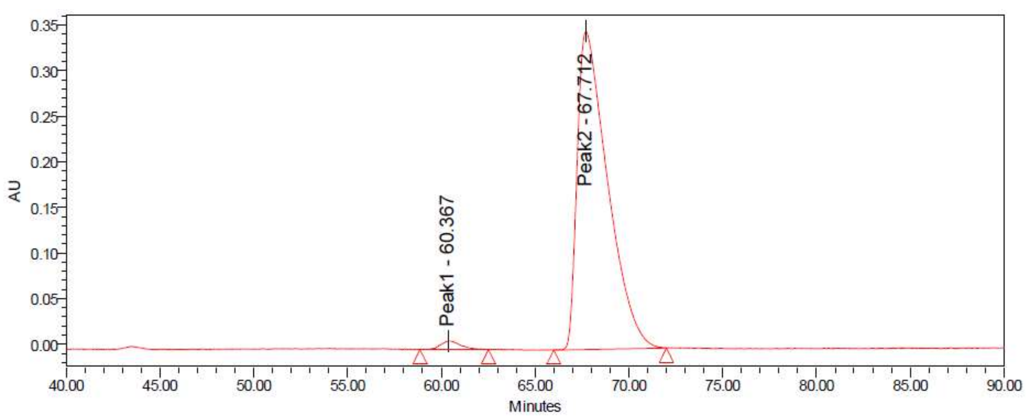
Reaction optimization in the presence of different catalytic systems

Entry-3



	Name	RT	Area	% Area
1	Peak1	58.25	453117	1.394
2	Peak2	65.65	32044349	98.606

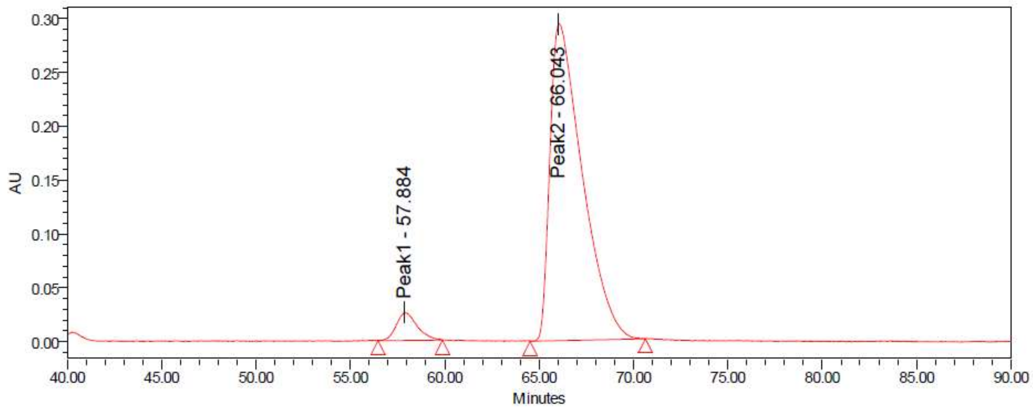
Entry-5



	Name	RT	Area	% Area
1	Peak1	60.37	716473	1.791
2	Peak2	67.71	39294888	98.209

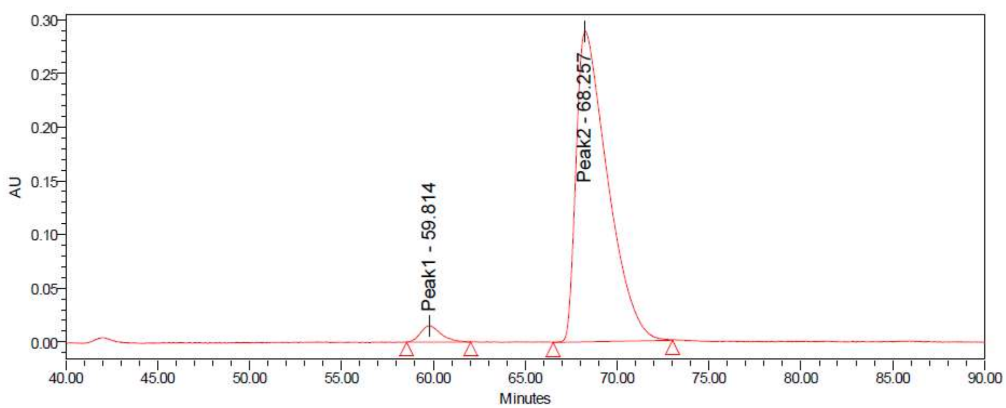
Reaction optimization in the presence of different solvent systems

Entry-1



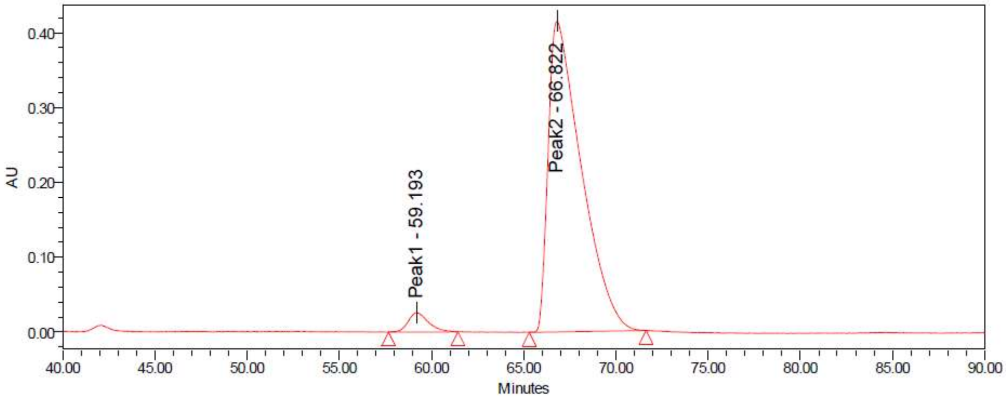
	Name	RT	Area	% Area
1	Peak1	57.88	1990346	5.375
2	Peak2	66.04	35041343	94.625

Entry-4



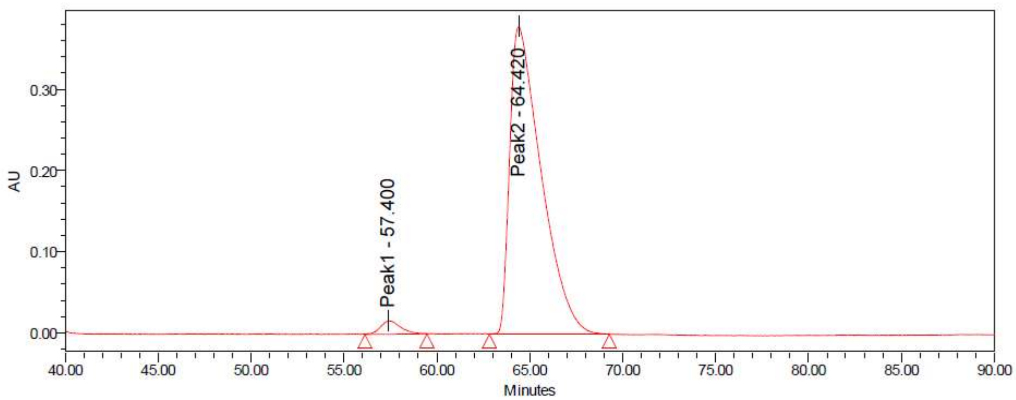
	Name	RT	Area	% Area
1	Peak1	59.81	1189175	3.335
2	Peak2	68.26	34471631	96.665

Entry-5



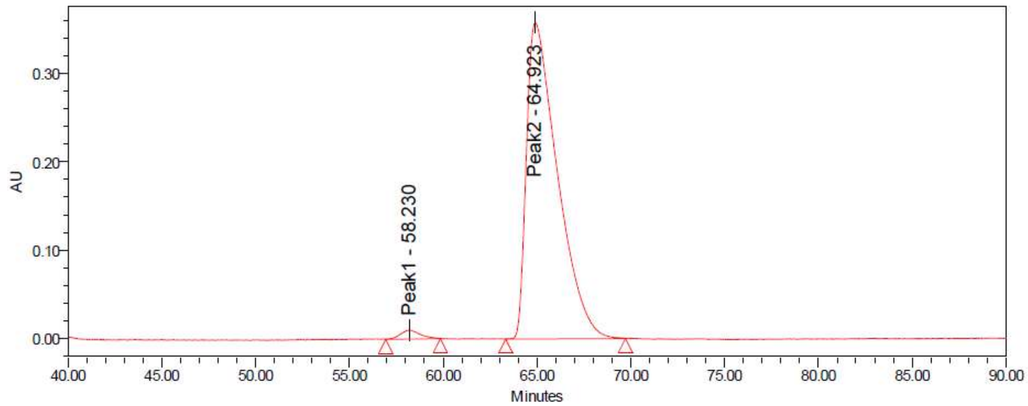
	Name	RT	Area	% Area
1	Peak1	59.19	1984799	3.688
2	Peak2	66.82	51827468	96.312

Entry-6



	Name	RT	Area	% Area
1	Peak1	57.40	1253372	2.735
2	Peak2	64.42	44565518	97.265

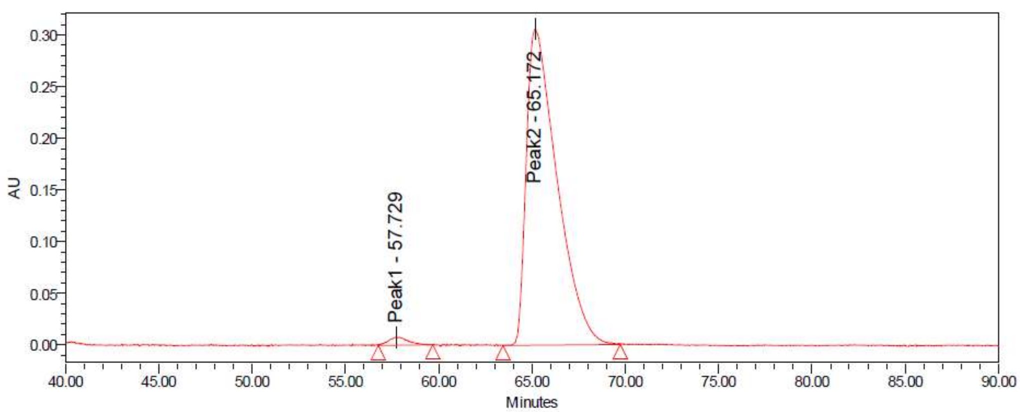
Entry-8



	Name	RT	Area	% Area
1	Peak1	58.23	743461	1.778
2	Peak2	64.92	41080646	98.222

Effect of temperature

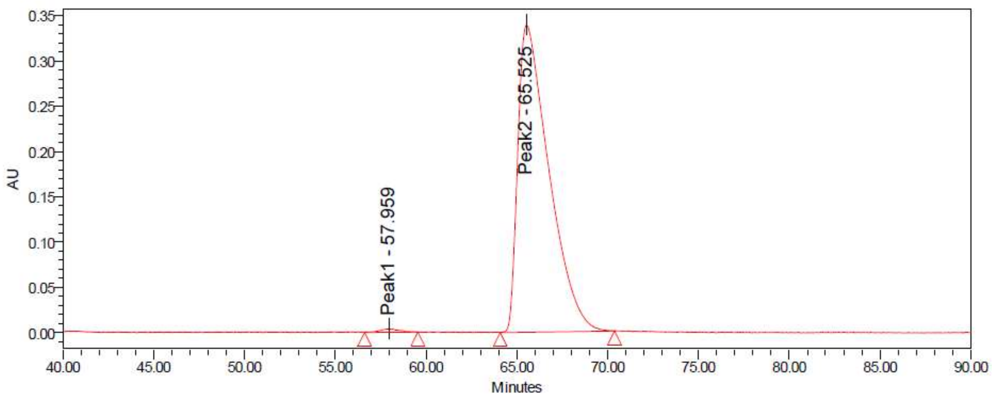
Entry -1



	Name	RT	Area	% Area	RT Ratio
	Peak1	57.73	576642	1.620	
	Peak2	65.17	35028335	98.380	

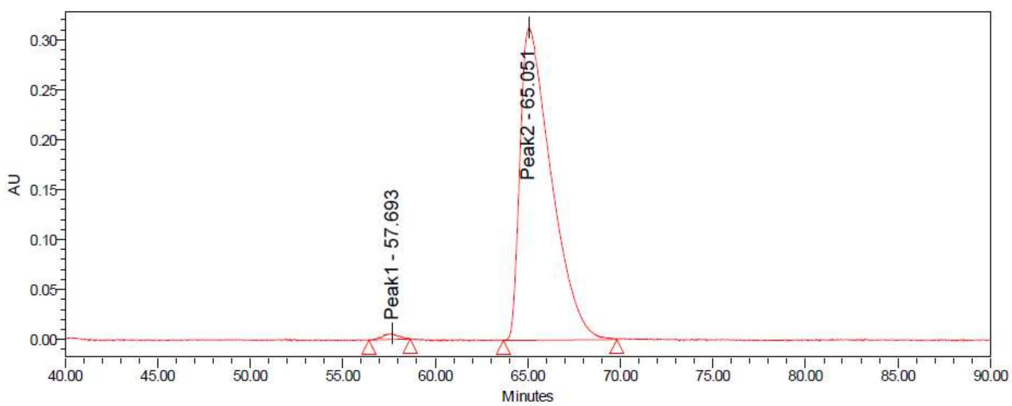
Recycling experiments:

Entry-2



	Name	RT	Area	% Area
1	Peak1	57.96	290023	0.713
2	Peak2	65.53	40404604	99.287

Entry-3



	Name	RT	Area	% Area
1	Peak1	57.69	362106	0.979
2	Peak2	65.05	36629395	99.021

5.4. 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.

5.5. References

1. Yusuke Muramatsu,Toshiro Harada Angew Chem Int Ed Engl. Volume47, Issue6, January 25, 2008, Pages 1088-1090.

2. Kenso Soai, Masami Watanabe, and Atsuhiro Yamamoto J. Org. Chem. 1990, 55, 16, 4832–4835.

3. M. Hatano, T. Mizuno, K. Ishihara, Synlett, 2010, 2024-2028.

4. Hiroshi Takahashi, Akihiro Kawabata, Hiroyuki Niwa, Kimio Higashiyama, Chem Pharm. Bull. 36(2), 803-806 (1988)

5. Da-Ming Du, Tao Fang, Jiaxi Xu, and Shi-Wei Zhang O*rg. Lett.* 2006, 8, 7, 1327–1330