4
Asymmetric Hydrogenation Catalysis

4.1 INTRODUCTION

As discussed in Chapter 2, heterogeneous catalysis has unique advantages over homogeneous catalysis. In asymmetric heterogeneous catalysis, the adsorption of chiral molecules on the surface of catalyst proved to be a successful strategy to develop chiral environment [Yoon and Jacobsen 2003]. Good chiral molecules usually have nitrogen close to one or more stereogenic centres and connected to a planer aromatic system [Bürgi and Baiker 2004, Hoxha *et al,* 2007]. Out of various studies on asymmetric heterogeneous catalysis, asymmetric hydrogenation of α-ketoesters is one of the key reactions with a wide range of applications (Figure 4.1).

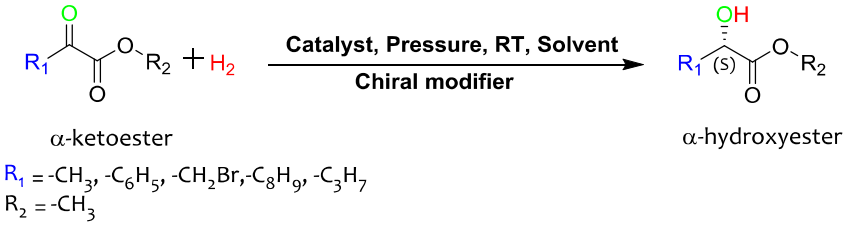


Figure 4.1 asymmetric hydrogenation reactions of α-ketoesters

The mechanistic details of asymmetric hydrogenation reaction of pyruvate has been described by numerous research groups [Garland and Blaser 1990, Blaser *et al,* 1991, Bartók and Szöllösi *et al,* 2002, Studer *et al,* 2003, Mallat *et al,* 2007]. Ortio *et al.* (in the period from 1979 to 1982) first reported the enantioselective hydrogenation of α-ketoesters catalyzed by Pt modified using cinchona alkaloids [Orito *et al,* 1979]. Further developments were carried out by Blaser, Baiker, Bartok and co-workers [Baiker 1997, Blaser and Jalett *et al,* 1997, LeBlond and Wang *et al,* 1999, Bartók *et al,* 2001, Lavoie *et al,* 2003, Bartók *et al,* 2005]. Inorganic oxides have been used as a supporting material in Pt-catalysed hydrogenation [Török and Felföldi *et al,* 1997, Toukoniitty and Murzin 2004, Xiong and Ma *et al,* 2005, Hong *et al,* 2015]. Although, these oxide supports show good catalytic activity, they are being replaced by carbon materials, due to some drawbacks of oxides as stated in Chapter 2 [Tauster and Fung *et al,* 1978]. Tungler *et al.* investigated the performance of carbon supported Pd and Pt catalysts in the asymmetric reduction of ethyl pyruvate, in the presence of cinchonidine, and found maximum 34% enantioselectivity, in the case of Pt catalyst [Tungler and Tarnai *et al,* 1991]. Li and co-workers [Chen and Guan *et al,* 2011] reported non-metal oxide supported asymmetric heterogeneous catalysis for hydrogenation of α-ketoesters, in which chiral modified Pt nanoparticles were supported on multi-walled carbon nanotubes. Good enantioselectivity was obtained at high pressure, with these supporting materials.

The cinchona modified platinum nanoparticles loaded on functionalized carbon materials were screened for hydrogenation of methyl pyruvate for the first time, in this work, and results are reported in this Chapter. Heterogenisation was achieved by the coordination between the chiral modifier and the Pt functionalized carbon surface. In the second study, hydrogenation of α-ketoesters over Pt HNC (111) loaded carbon materials was screened. In third study, Pt loaded polyamide were used for asymmetric hydrogenation reaction of ethyl-

oxo-4-phenylbutanote. Possible interactions in between reaction components, during the hydrogenation reaction, are also described in this chapter.

In brief, the main focus was to produce chiral compounds by reduction of α-ketoesters in the presence of heterogeneous catalysts (Pt/C, Pt HNC/C and Pt/Chiral polyamide) prepared by loading of transition metals on different supporting materials (Chapter 3).

4.2 ASYMMETRIC HYDROGENATION OF METHYL PYRUVATE ON THE SURFACE OF Pt/C CATALYSTS

4.2.1 Earlier Work

The hydrogenation of methyl pyruvate by platinum modified heterogeneous catalysts was reviewed earlier (Figure 4.2), the first hydrogenation of methyl pyruvate was carried out in ethanolic solution over 6.3% Pt/silica at 293 K [Orito *et al,* 1979, Sutherland *et al,* 1990, Meheux *et al,* 1991]. Later, other metal supported catalysts were tested for asymmetric hydrogenation reaction of methyl pyruvate [Sermon and Azhari 1990, Minder and Schürch *et al,* 1996, Pfaltz and Heinz 1997]. The effect of modifiers and solvents on enantioselectivity and reaction rate was also reported [Bond *et al,* 1991, Wilhelmus 1993, LeBlond *et al,* 2000, Li *et al,* 2004].

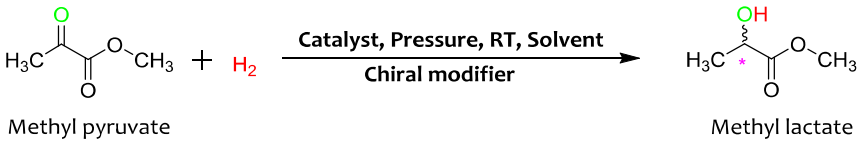


Figure 4.2 Asymmetric hydrogenation reaction of methyl pyruvate

The catalyst-substrate complex was explained by kinetic studied and an important role of a complex in enantioselectivity process was found [Bhaduri *et al,* 2000]. The effect of interaction between substrate and modifier on enantioselectivity was also reported [Rauls and Hammer 2006]. Chiral modifiers like codeine, brucine and strychnine have been tested in enantioselective hydrogenation of methyl pyruvate [Blaser and Jalett *et al,* 1991, Wilhelmus 1994, Blaser *et al,* 2000]. The chemical and optical yields reported in these studies are quite encouraging. These studies motivated us to test carbon based materials (activated carbon, graphene, carbon fiber and multiwall carbon nanotubes) as supports for Pt based heterogeneous catalysis.

4.2.2 Our Work

A detailed study was carried out on asymmetric hydrogenation of methyl pyruvate in acetic acid using Pt/C (MWCNTs, CF, AC and graphene) catalytic systems for achieving better insight in such transformations (Figure 4.3). The chiral modifier was absorbed on the surface of Pt functionalized carbon catalyst and created an asymmetric environment. Substrate-modifier interactions can be explained by time dependent NMR studies.

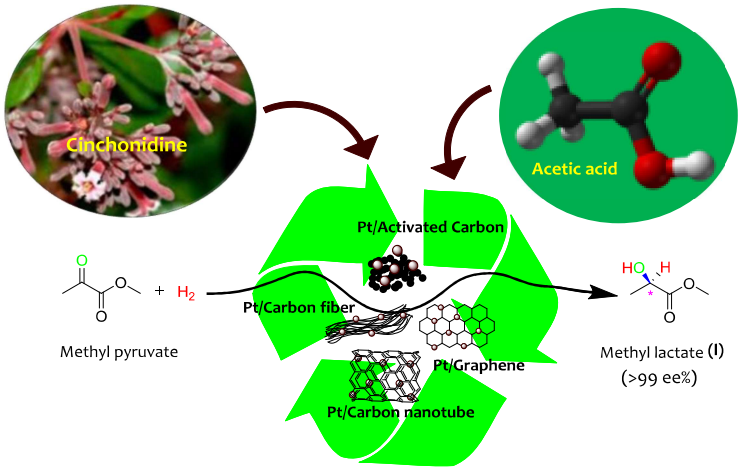


Figure 4.3 Asymmetric hydrogenation reaction of methyl pyruvate over Pt/C

4.2.3 Experimental

General Remarks

Catalytic asymmetric hydrogenation reaction was carried out in a Berghof HR-100 high pressure vessel equipped with a Teflon container. Methyl pyruvate (98 % assay) and cinchonidine (99 % total base) were received from Alfa Aesar. Acetic acid (Fisher scientific, 99.9 %), platinum on activated carbon (Across, 5 % Pt) and ethanol (commercial grade) were commercially obtained. High purity dry hydrogen and argon (99.999%) gases were used from local resources. Chromatographic resolutions of the enantiomers were carried out on a normal phase CHIRALPAK ID (Lot No.ID00CE-PL014) type chiral column under isocratic and isothermal (at 30˚C) conditions using the mixture of n-hexane/iso-propanol as the mobile phase. The preparation and characterization of Pt loaded carbon catalysts are given in Chapter 3**.** Analytical techniques that were used for characterization of products are described in Chapter 3**.**

General Process for Asymmetric Hydrogenation of Methyl Pyruvate

A process for asymmetric hydrogenation of methyl pyruvate was used to optimize the reaction conditions, the hydrogenation of methyl pyruvate (0.8 mmol) was carried out in acetic acid (2.3 mL) using commercially available 5 % Pt/AC, at room temperature, by varying the pressure (Table 4.1). The highest conversion was obtained at 70 bar pressure. Further, at high pressure, the reaction conversion decreased due to competitive absorption of H_2 molecule. In absence of a chiral modifier, a racemic mixture of methyl lactate was obtained, where in presence of cinchonidine, the R-(+)-enantiomer was formed.

Under optimized conditions (Entry 7, Table 4.1), other catalysts were also tested (Table 4.2). Pt loaded carbon catalysts were pre-treated in a tubular a furnace under hydrogen flow, for 3 h at 300 ˚C, prior to reaction. These reactions were carried out at large scale. For the reactions, Pt/C (300 mg), chiral modifier (Cinchonidine, 40 mg, 0.13 mmol), and acetic acid (15 mL, 23.7 mmol) were premixed in teflon lined stainless steel vessel under hydrogen, and after 10 minutes methyl pyruvate (0.75 mL, 8.3 mmol) was introduced.

Table 4.1 Optimization of reaction conditions using commercial Pt loaded activated carbon (Pt/AC) for hydrogenation of methyl pyruvate

Entry	Pressure (bar)	Yield [a] (%)
1	10	60
2	20	80
3	30	90
4	40	92
5	50	94
6	60	96
7	70	97
8	80	90

[a]Reaction was carried out using 5 % Pt/AC (4 mg) methyl pyruvate (0.8 mmol) and acetic acid (2.3 mL) for 4 h, at room temperature. Racemic mixtures of the products were obtained.

The reaction mixture was purged with hydrogen 2-3 times to remove the air and filled under the desired pressure (10-80 bar; Caution of pressurized hydrogen!) followed by stirring for 4 h. Subsequently, the reaction mixture is centrifuged to obtain the crude product. The product is purified via bulb to bulb distillation and analysed by ^{1}H NMR and HPLC. When the same reaction was carried out in the absence of cinchonidine, a racemic product was obtained (A5). The % yield was calculated by weighing the final purified product, on a balance (Mettlar Toledo-ML204) with the accuracy of 0.1 mg. The reaction was scaled up to 10 g.

Table 4.2 Asymmetric hydrogenation of methyl pyruvate using various catalytic systems[a]

Entry	Catalyst	Yield (%)	*ee* [b] (%)
1	Pt/AC	97	31
2	Pt/Graphene	87	91
3	Pt/Carbon Fibre	75	89
4	Pt/MWCNT	99	>99

[a]The Pt loading for all catalyst was 5 wt %. Reaction conditions: methyl pyruvate/acetic acid/Cinchonidine/hydrogen pressure/time/temperature: 0.75 mL/15 mL/40 mg/70 bar/4 h/RT.
[b]Determined by HPLC analysis using a CHIRALPAK ID chiral column.

Among these catalytic systems, the Pt/MWCNTs catalyst proved to be the most effective in terms of product yield and enantioselectivity i.e., >99% ee, which is the highest for supported catalytic asymmetric hydrogenation of methyl pyruvate.

(R)–(+)–Methyl Lactate

^{1}H NMR ($CDCl_3$, 500 MHz) (>99 %): δ 1.41 (d, 3 H, J = 7.05 Hz, CH_3), 2.93 (d, 1 H, J = 5 Hz OH, D_2O exchangeable), 3.79 (s, 3 H, CH_3), 4.29 (q, 1 H, J = 6.94 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): 20.0, 52.2, 66.7, 175.7 ppm, $[\alpha]_D^{20^\circ C}$ = +8.9 (c 1.5, 1, 4-dioxane) 41; IR (KBr) 3346, 2975, 1710, 1379, 1266, 1084, 1052, 831 cm^{-1}. Retention time: 2.9 min for (R)-(+)-methyl

lactate, 3.4 min for (S)-(-)-methyl lactate. UV-vis (CH_3COOH) gave absorbance at 210-250 nm. Selective chromatograms are given in annexure (A1-A4).

4.3 ASYMMETRIC HYDROGENATION OF α-KETOESTER ON THE SURFACE OF Pt (111) HNC/C CATALYSTS

4.3.1 Earlier Work

In earlier studies, great efforts were made to obtain maximum enantioselectivity, by optimizing pressure, temperature, solvent, catalyst and modifier [Minder and Schürch *et al,* 1996]; but little attention was given to the metal characteristics constitutes (shape and crystallographic facets) and their effect on enantioselectivity, and rate of reaction. Metal characteristics can also affect the activity of catalyst. Among several characteristics, shape and size dependent catalytic activity have been studied in a wide range of reactions, which include hydrogenations [Pradier and Birchem *et al,* 1994, Borodziński 2001, Molnár *et al,* 2001], oxidations [Arenz and Mayrhofer *et al,* 2005, Sen and Gökagaç 2007], Suzuki [Li and Boone *et al,* 2002] and Heck [Le Bars *et al,* 1999] couplings among others[Blaser and Garland *et al,* 1993, Studer and Burkhardt *et al,* 2000, Narayanan and El-Sayed 2004]. Various shapes of metal expose special planes of a crystal structure. Among the large class of metal planes, the Pt planes play an important role in asymmetric hydrogenation reaction. In literature, highly faceted Pt supported on carbon showed outstanding catalytic performances in different applications [Narayanan and El-Sayed 2004, Somorjai and Park 2008, Lin and Chu *et al,* 2009, Zhou and Li 2012]. Out of the different planes of the Pt, Pt (111) has highly catalytic activity in various reactions, due to its higher packing density, stability and cohesive energy, that are responsible for significant chemisorptions of a variety of chemical entities [Laliberté and Lavoie *et al,* 2008, Somorjai and Park 2008, Schmidt and Vargas *et al,* 2009, Demers-Carpentier and Rasmussen *et al,* 2013].

4.3.2 Our Work

The highly faceted and dispersed Pt (111) hexagonal nanocrystals loaded on carbon catalysts (MWCNTs, CF, activated carbon and graphene) were screened for asymmetric hydrogenation of α-ketoesters using cinchonine. The activity of Pt (111) nanocrystal was examined for achieving enhanced insight in asymmetric catalysis (Figure 4.4).

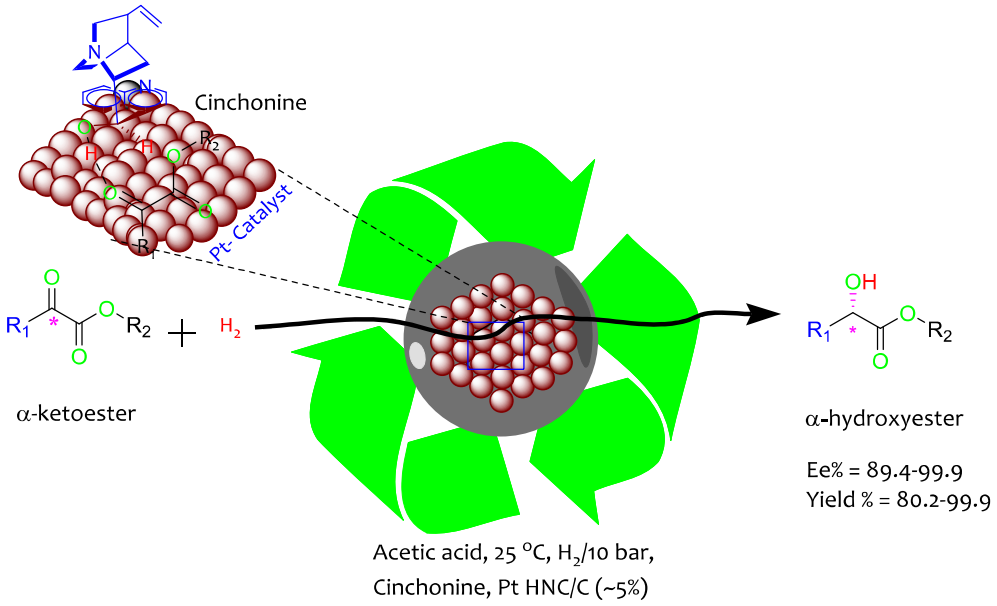


Figure 4.4 Asymmetric hydrogenation reaction of α-ketoester over Pt (111) HNC/C

4.3.3 Experimental

General Remarks

Ethyl pyruvate (98 %), ethyl 3-bromo-2 oxopropanoate (90 %, Aldrich), ethyl 3-methyl-2-oxobutanoate (97 %, Aldrich), ethyl 2-oxo-4-phenylacetate (95 %, Aldrich), ethyl 2-oxo-4-phenylbutanoate, cinchonine (CN, ≥98 %), and tetraoctyl ammonium bromide (98 %) were received from Sigma Aldrich. Acetic acid (99.8 %), toluene, tetrahydofurane and ethyl alcohol were purchased from a local source. Chromatographic resolutions of the enantiomers were carried out on a normal phase. The characterization and preparation procedure of Pt hexagonal nanocrystals loaded carbon catalysts are specified in Chapter 3. Chemical shift for ^{1}H NMR spectra are reported as δ in parts per million (PPM) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet).

General Procedure for Hydrogenation over Pt HNC/C

Reaction conditions were optimised with Pt HNC/MWCNT at different pressures, in various solvent (Table 4.3) and it was found maximum enantioselectivity at 10 bar in acetic acid.

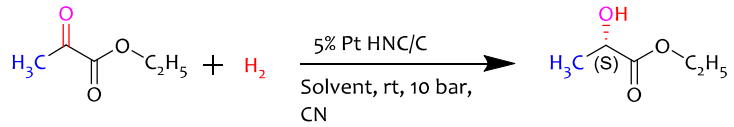
Table 4.3. Asymmetric catalytic hydrogenation reaction on Pt HNC/MWCNT

Entry	Catalyst[a]	Time (h)	H_2Pressure (bar)	Conversion (%)[b]	Solvent
1	Pt HNC/MWCNT	24	1	20	Acetic acid
2	Pt HNC/MWCNT	24	5	70.4	Acetic acid
3	Pt HNC/MWCNT	24	10	99.9	Acetic acid
4	Pt HNC/MWCNT	24	15	99.1	Acetic acid
5	Pt HNC/MWCNT	24	20	98.5	Acetic acid
6	Pt HNC/MWCNT	12	10	99.9	Acetic acid
7	Pt HNC/MWCNT	6	10	82.2	Acetic acid
8	Pt HNC/MWCNT	12	10	30.3	THF
9	Pt HNC/MWCNT	12	10	45.8	Toluene
10	Pt HNC/MWCNT	12	10	25.6	Ethyl alcohol

[a]Catalysts prepared with 5 wt% metal loading. All the reactions were performed by using 30 mg Pt HNC/MWCNT and 75 µL ethyl pyruvate under different pressures in different solvents by varying time.
[b]Conversion was investigated by NMR and HPLC.

Under optimized reaction conditions, hydrogenation of ethyl pyruvate was carried out in the presence of other Pt HNC supported carbon materials, where Pt HNC/MWCNT was found to be the most active catalytic system in terms of chemical and optical selectivity (Table 4.4).

Table 4.4. Asymmetric hydrogenation reaction of ethyl 2-oxopropanoate on various Pt HNC/C catalysts[a]



Ethyl 2-oxopropanoate — Ethyl (S)-2-hydroxypropanoate

Entry	Catalysts	Yield %[b]	Ee %[c]
1	Carbon materials	<10	0
2	Pt HNC/MWCNT	99.9	99.6
3	Pt HNC/AC	99.0	94.6
4	Pt HNC/Graphene	97.5	96.8
5	Pt HNC/CF	92.4	89.4

[a]Proposed reaction conditions: RT: 25°C; Pt HNC/C catalyst: 30 mg, reaction time: 12 h; ethyl pyruvate: 75 µL; CN: 4 mg; acetic acid: 1.5 mL. [b]Isolated by bulb to bulb distillation. [c]Determined by HPLC analysis (A7).

Varying the substrate, different functionalized α-ketoesters were screened with the Pt HNC/MWCNT catalyst (Table 4.5, Figure 4.5). Surprisingly, all derivatives gave high conversion and enantioselectivity, except bromo derived esters, probably due to catalytic poisoning by bromide [Menzel *et al,* 2000]. Maximum conversion (99.8 %) and enantioselectivity (~99.9 %) was found in case of methyl 2-oxopropanoate.

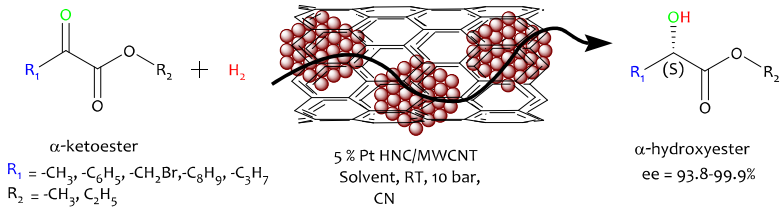


Figure 4.5 Asymmetric hydrogenation reaction of various α-ketoester over Pt (111) HNC/MWCNT

In a typical process, catalysts were prehydrogentated at 300°C for 3 h in hydrogen atmosphere before hydrogenation reaction. In a typical procedure, asymmetric hydrogenation reaction was carried out in a high pressure vessel (Berghof HR-100) equipped with a Teflon container. A reaction mixture of 30 mg catalyst, 75 µL α-ketoester, 4 mg (0.01 M) CN and 1.5 mL (17.5 M) acetic acid were added. Vacuum was created in the vessel, followed by purging hydrogen gas under the maintained pressure of 10 bars, for 12 h, at room temperature. The reaction mixture was centrifuged to obtain the crude product and was purified via bulb to bulb distillation (Glass Oven B-585 Kugelrohr). The yield was calculated by weighing the final purified product; using a balance (Mettlar Toledo-ML204) with an accuracy of 0.1 mg. Reaction conversion and enantiomeric excess were monitored by NMR and HPLC (A6-A11), respectively.

Table 4.5. Asymmetric hydrogenation reaction of pyruvate derivative on Pt HNC/MWCNT

Entry[a]	Substrate	Yield %	Ee %
1	Ethyl 3-bromo-2-oxopropanoate	80.2	93.8
2	Ethyl 3-methyl-2-oxobutanoate	90.4	98.7
3	Ethyl 2-oxo-4-phenylacetate	92.7	99.6
4	Ethyl 2-oxo-2-phenylbutanoate	94.4	99.0
5	Methyl 2-oxopropanoate	99.8	~99.9

[a]Reaction conditions and analysis similar to those given in Table 4.4.

Product analysis

Methyl 2-hydroxypropanoate (I)

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.41 (d, 3 H, J = 7.05 Hz, CH_3), 2.93 (d, 1 H, J = 5 Hz OH, D_2O exchangeable), 3.79 (s, 3 H, CH_3), 4.29 (q, 1 H, J = 6.94 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): 20.0, 52.2, 66.7, 175.7 ppm, $[\alpha]_D^{20^\circ C}$ = +8.9 (c 1.5, 1, 4-dioxane); IR (KBr) 3346, 2975, 1710, 1379, 1266, 1084, 1052, 831 cm^{-1}. Optical purity determined by HPLC (245 nm); Daicel Chiral Cell CHIRALPAK ID 0.46 cm/25 cm; hexane/iso-propanol/$Na_2B_2O_7$ = 90/10/0.1; flow rate = 0.8 mL/min; Retention time: 3.0 min for (R)–(+)–methyl 2-hydroxypropanoate, 4.0 min for (S)–(–)–methyl 2-hydroxypropanoate (A6).

Ethyl-(S)-2-hydroxypropanoate (II)

^{1}H NMR; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.28 (3 H, t, *J* = 7.34 Hz, CH_3), 1.42 (3 H, d, *J* = 6.90 Hz, CH_3), 4.21 (2 H, q, *J* = 7.09 Hz, CH_2), 4.26 (1H, q, *J* = 6.85 Hz, *CH*), ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): 14.01, 20.6, 61.6, 66.7, 175.8 ppm; $[\alpha]_D^{20^\circ C}$ = +10 (c 0.1 in ethanol) [Feenstra *et al,* 1988]. Optical purity determined by HPLC (245 nm); Daicel Chiral Cell CHIRALPAK ID 0.46 cm/25 cm; hexane/iso-propanol/$Na_2B_2O_7$ = 90/10/0.1; flow rate = 1.0 mL/min; Retention time: 3.1 min for (R)–(+)–methyl 2-hydroxypropanoate, 4.3 min for (S)–(–)–methyl 2-hydroxypropanoate **(**A7**).**

Ethyl 2-hydroxy-3-methylbutanoate (III)

^{1}H NMR; δ_H (500 MHz; $CDCl_3$; Me_4Si) 0.86 (6 H, d, *J* = 7.15 Hz, CH_3), 1.36 (3 H, t, *J* = 6.87 Hz, CH_3), 3.26 (1 H, m, *J* = 7.47 Hz, *CH*), 4.04 (1 H, d, *J* = 3.53 Hz, *CH*), 4.26 (2 H, q, *J* = 7.07 Hz, CH_2), ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): 14.1, 18.6, 32.1, 61.6, 75.6, 175.08 ppm; $[\alpha]_D^{20^\circ C}$ = -8.3 (c 0.1 in chloroform) [Inoue *et al,* 2005]. Optical purity determined by HPLC (220 nm); Daicel Chiral Cell CHIRALPAK ID 0.46 cm/25 cm; hexane/iso-propanol/EtOAc = 98/1.5/0.5; flow rate = 1.0 mL/min; Retention time: 3.0 min for (R)–(+)–ethyl 2-hydroxy-3-methylbutanoate, 4.6 min for (S)–(–)–ethyl 2-hydroxy-3-methylbutanoate **(**A8**).**

Ethyl 2-hydroxy-2-phenylacetate (IV)

^{1}H NMR; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.21 (3 H, t, *J* = 7.45 Hz, CH_3), 4.21 (2 H, q, *J* = 3.45 Hz, CH_2), 5.19 (1 H, s, *CH*), 7.29 (5 H, m, *J* = 6.85 Hz, C_4H_5), ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): 14.0, 61.6, 72.8, 126.8, 127.5, 129.5, 138.2, 173.7 ppm; $[\alpha]_D^{20^\circ C}$ = +10 (c 0.1 in chloroform). Optical purity is determined by HPLC (254 nm); Daicel Chiral Cell CHIRALPAK ID 0.46 cm/25 cm; n-hexane/iso-propanol/TFA = 98/1.99/0.01; flow rate = 0.5 mL/min; Retention time: 3.2 min for (R)–(+)–ethyl 2-hydroxy-2-phenylacetate, 4.4 min for (S)–(–)–ethyl 2-hydroxy-2-phenylacetate **(**A9**).**

Ethyl 3-bromo-2-hydroxypropanoate (V)

^{1}H NMR; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.21 (3 H, t, *J* = 7.20 Hz, CH_3), 3.17 (2 H, d, *J* = 7.05 Hz, CH_2), 4.06(2 H, q, *J* = 7.27 Hz, CH_2), 5.04 (1 H, t, *J* = 7.17Hz, *CH*) ppm; ^{13}C NMR ($CDCl_3$, 125

MHz): 13.9, 35.4, 60.6, 82.7, 170.8 ppm; $[\alpha]_D^{20^\circ C}$ = -19.01 (c 0.1 in chloroform). Optical purity determined by HPLC (254 nm); Daicel Chiral Cell CHIRALPAK QD-AX 0.46 cm/15 cm; Methanol/Acetic acid/Ammonium acetate = 98/1.5/0.5 (v/v/w); flow rate = 0.5 mL/min; Retention time: 2.1 min for (R)−(+)−ethyl 3-bromo-2-hydroxypropanoate, 3.7 min for (S)−(−)−ethyl 3-bromo-2-hydroxypropanoate **(**A10**).**

Ethyl 2-hydroxy-4-phenylbutanoate (VI)

^{1}H NMR; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.36 (3H, t, *J* = 7.11 Hz, CH_3), 2.9 (2H, m, *J* = 7.36 Hz, CH_2), 3.16 (2H, t, *J* = 7.15 Hz, CH_2), 4.25 (2H, q, *J* = 7.22 Hz, CH_2), 4.33 (1H, t, *J* = 7.52, *CH*), 7.19(5H, m, *J* = 7.48 Hz, C_4H_5), ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): 14.1, 35.8, 61.7, 70.0, 126.0, 128.3, 128.5, 141.1, 175.3, ppm; $[\alpha]_D^{20^\circ C}$ = +16.5 (c 0.1 in chloroform)[Satoh *et al,* 1990]. Optical purity determined by HPLC (254 nm); Daicel Chiral Cell CHIRALPAK QD-AX 0.46 cm/15 cm; n-hexane/iso-propanol/TFA = 98/1.5/0.5 (V/V/W); flow rate = 0.8 mL/min; Retention time: 4.9 min for (R)−(+)−ethyl 2-hydroxy-4-phenylbutanoate, 5.6 min for (S)−(−)−ethyl 2-hydroxy-4-phenylbutanoate **(**A11**).**

4.4 ASYMMETRIC HYDROGENATION OF ETHYL 2-OXO-4-PHENYLBUTANOATE ON THE SURFACE OF Pt LOADED CHIRAL POLYAMIDE

4.4.1 Earlier Work

Carbon materials are often functionalized before Pt loading. Thus, an extra effort is needed in case of asymmetric hydrogenation reaction over Pt loaded carbon catalysts. For functionalisation, strong acids are required. In Pt loaded carbon catalysts, a chiral source is needed for chiral induction. The chiral source leaches out after each cycle and needs to be added after every cycle, to obtain maximum enantioselectivity. To reduce these above efforts, it was found that the metal on polymer have seen the resurgence of catalytic activity. Since the first report by Izumi, in 1956, of palladium-protein complex adsorbed on silk fibroin, as a catalyst for asymmetric hydrogenation of oxo-glutarates [Akabori *et al,* 1956, Izumi 1959], Huang et al. carried out enantioselective hydrogenation of ethyl pyruvate catalyzed by poly (vinylpyrrolidone)-stabilized rhodium nanocluster (Rh/PVP) modified by cinchonidine and quinine [Teichner and Hoang-Van *et al,* 1982, Huang and Chen *et al,* 2001]. Pt loaded polymer catalyst was also used for asymmetric hydrogenation reaction [Michalska and Ostaszewski *et al,* 2002].

In heterogeneous asymmetric catalysis, it has been established that chirality could be transferred from chiral ligands, metal-chiral ligand complex and immobilized chiral polymers [Fan *et al,* 2002, Itsuno *et al,* 2005, Islam and Ahamed *et al,* 2014, Itsuno and Hassan 2014]. Additionally, polymer surface and specific configuration play important roles in chiral induction by offering precise places for adsorbing or dissociating the substrates [Amabilino 2016]. Polyamide is a polymer surface with catalytic sites, assembled in a specific configuration, which make a helical shape. Thus, the chirality may be derived from a chiral monomer or polymer helicity, as observed in optically active helical polymers [Jiang *et al,* 2016]. The helical polymer backbones demonstrate "chiral amplification" effects and promise a variety of practical applications in asymmetric catalysis and recognition [Yashima *et al,* 2009, Du *et al,* 2010, Zhang *et al,* 2012]. Further, the catalytic activity of supported single crystals of metallic nanoparticles has been in focus [Bruix *et al,* 2014, Zhao *et al,* 2014], due to the unique advantages, such as low coordination, effective metal-support interaction and quantum size effect, which significantly improves the catalytic performance [Zhang *et al,* 2015]. A combination of chiral polymer with isolated single metal atom could serve as an ideal heterogeneous catalytic system. Interaction studies of platinum with amide have been distinctly investigated earlier [Forbes *et al,* 2013], assuming metal ligand interaction without varying oxidation state of platinum [Imelik 2000].

4.4.2 Our Work

The significant potential of Pt loaded chiral helical polyamide was tested for asymmetric hydrogenation of ethyl 2-oxo-4-phenylbutanoate (Figure 4.6). The preparation and characterization of Pt loaded chiral polyamides are discussed in Chapter 3.

Pt/Chiral polyamides transfer the chirality to the product via helical structure. Thus, the polyamide helical backbone serves as an external chiral source, by helping in chiral induction, and amide group of polyamide can overcome the problems related to the activation of the support.

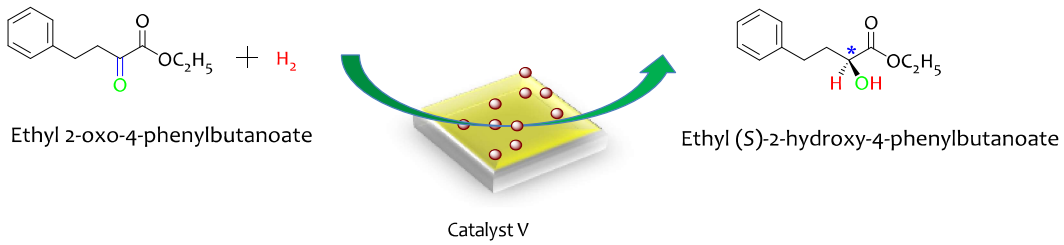


Figure 4.6. Asymmetric hydrogenation of ethyl 2-oxo-4-phenylbutanoate

4.4.3 Experimental

General Remarks

Thionyl chloride ($SOCl_2$), chloroform and hexane were commercially available. Ethyl 2-oxo-4-phenylbutanoate (98%), hexamethyelenediamine, 1, 3 diaminopropane, 1, 4 diaminobutane, 1, 5 diaminopetane, ethylenediamine, hexachloroplatinic acid (37.50 % Pt basis) and D-camphoric acid were received from Sigma Aldrich. Toluene was purchased from Fisher Scientific. Chromatographic resolutions of the enantiomers were carried out on a normal phase CHIRALPAK ID (Lot No.ID00CE-PL014) type chiral column under isocratic and isothermal (at 30°C) conditions using a mixture of n-hexane/iso-propanol as the mobile phase. The preparation and characterization of Pt loaded polyamide are given in Chapter 3.

General Procedure for Hydrogenation over Pt Loaded Chiral Polyamide

The hydrogenation reaction was optimized for ethyl 2-oxo-4-phenylbutanoate, using catalyst V, and maximum conversion, and yield was obtained at 25 bars in 5 minute (Table 4.6).

Table 4.6 Optimization of reaction conditions using catalyst V for asymmetric hydrogenation of ethyl 2-oxo-4-phenylbutanoate[a]

S. No.	Pressure (bars)	Yield (%)[b]
1	5	20.5
2	10	35.3
3	15	70.8
4	20	82.2
5	25	99.7
6	30	96.1

[a]The reaction was carried out using 5 wt%. Catalyst V (10 mg) and ethyl 2-oxo-4-phenylbutanoate (0.20 mL) for 5 min at 25°C. [b]Isolated yield.

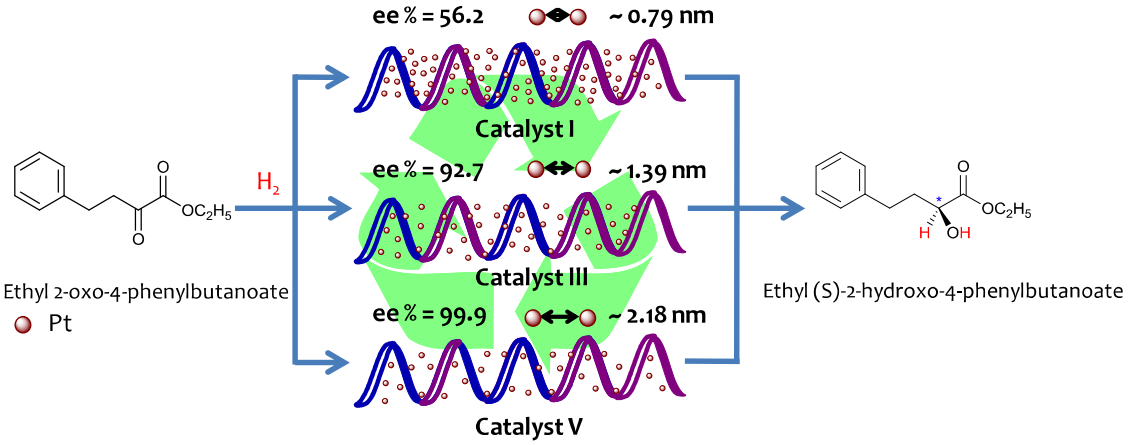
Other Pt loaded chiral polyamide catalysts were tested (Table 4.7). The catalytic asymmetric hydrogenation reaction was carried out in a Berghof HR-100 high pressure vessel

equipped with a Teflon container. Catalyst (10 mg, in Teflon stencil) was placed in high pressure reactor and purged 5 times with H_2 gas, ethyl 2-oxo-4-phenylbutanoate (0.20 mL) was added and pressure was maintained at 25 bars for 5 min. After catalytic reaction, the product was separated from the catalyst surface by washing thoroughly with chloroform. The given conversion and isolated yield are the average of five reactions, carried out under identical conditions. Catalyst V gave complete conversion and excellent enantioselectivity (> 99.9 %) due to high dispersion of Pt nanoparticles on the surface of chiral polyamide. The conversion and optical purity were analyzed by NMR and HPLC (A12-A17), respectively. In the absence of chiral polyamide, a racemic product was obtained (A12**).** There could be two viable ways of chirality transfer, first the chiral polyamides containing chiral monomer units having two chiral centres, and second, the chirality transfer from the helices to the catalytically active platinum centre. It is noteworthy that effective optical induction occurs on achiral metal centres located at its periphery and this has a major role in asymmetric catalysis [Berova and Nakanishi 2000, Takahashi *et al,* 2009, Busch and Busch 2011, Itsuno 2011].

Product Analysis (VI)

^{1}H NMR; δ H (500 MHz; $CDCl_3$; Me_4Si) 1.36 (3H, t, J = 7.11 Hz, CH_3), 2.9 (2H, m, J = 7.36 Hz, CH_2), 3.16 (2H, t, J = 7.15 Hz, CH_2), 4.25 (2H, q, J = 7.22 Hz, CH_2), 4.33 (1H, t, J = 7.52, CH), 7.19 (5H, m, C_4H_5), ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): 14.1, 35.8, 61.7, 70.0, 126.0, 128.3, 128.5, 141.1, 175.3, ppm; Optical purity determined by HPLC (254 nm); Daicel Chiral Cell CHIRALPAK ID 0.46 cm/25 cm; hexane/iso-propanol/$Na_2B_2O_7$ = 90/10/0.1; flow rate = 1.0 mL min^{-1}; retention time: 4.9 min for R-(+)-ethyl 2-hydroxy-4-phenylbutanoate, 5.6 min for (S)-(-)-ethyl 2-hydroxy-4-phenylbutanoate (A12-A17). $[\alpha]_D^{20^\circ C}$ = -18.7 (c 0.1 in chloroform) [Satoh and Onda *et al,* 1990, Greenfield 2006].

Table 4.7 Asymmetric hydrogenation of ethyl 2-oxo-4-phenylbutanoate using different catalysts[a]



S. No.	Catalysts	Conversion/Yield (%)[b]	ee[c] (%)
1	I	87/83	56.2
2	II	90/82	80.4
3	III	93/85	92.7
4	IV	97/95	99.0
5	V	100/99.5	> 99.9

[a]Pt loading on all catalyst was 5 wt%. Reaction conditions, catalyst/ ethyl 2-oxo-4-phenylbutanoate/hydrogen pressure/time/ temperature: 10 mg/ 0.20 mL/ 25 bar/ 5 min/ RT. Determined by HPLC analysis using a CHIRALPAK ID chiral column. [b]Isolated yield by bulb to bulb distillation. [c]The optical yield was expressed as the enantiomeric excess (ee) of S-(-) enantiomer % ee = ([S]-[R])/([R]+ [S]) × 100 (A12-A17).

4.5 POSSIBLE INTERACTION BETWEEN SUBSTRATE, CATALYST, MODIFIER AND SUPPORTING MATERIALS

4.5.1 Possible Interaction Model of Substrate and Chiral Modifier in Asymmetric Hydrogenation Reaction

The interaction between substrate and modifier is mainly responsible for chirality. The interaction between modifier and substrate has been previously reported [Schwalm and Weber *et al,* 1993, Bartók and Felföldi *et al,* 1998, Rauls and Hammer 2006, Martinek *et al,* 2007, Taskinen and Nieminen *et al,* 2007]. Various interactions brought the stereogenic centre of cinchona close enough to the substrate, to achieve a high enantioselectivity of 99%. A pictorial hypothesis of the intermediate is shown in Figure 4.7, where a seven member transition state with both stereogenic centres of cinchonidine is being proposed. In this interaction substrate, carbonyl interacts with an absorbed hydrogenation molecule and is reduced.

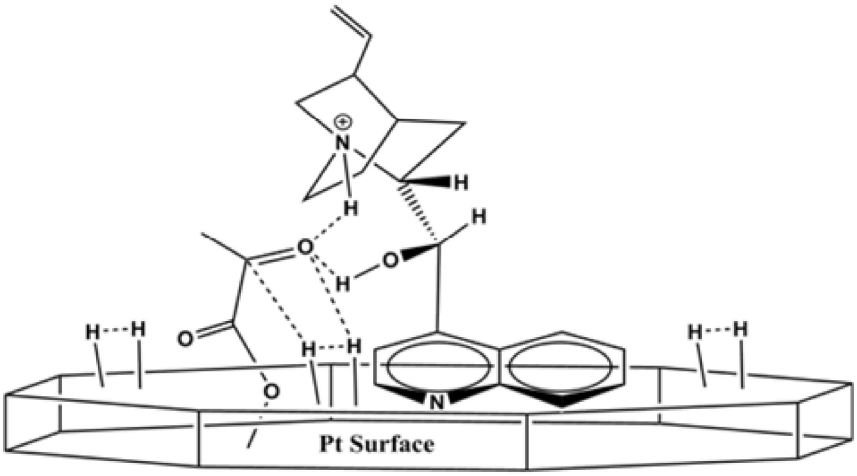


Figure 4.7 Intermediate structure of asymmetric hydrogenation reaction of methyl pyruvate with cinchonidine on the catalyst surface

To confirm the interaction between substrate and chiral modifier, a time depended NMR study was carried out. The in-situ ^1H NMR was recorded in toluene-d_8 as the reaction progressed to understand the substrate-modifier interactions. It is generally believed that cinchonidine, substrate and hydrogen are absorbed on the Pt surface, which leads to the enantioselectivity [Schwalm and Minder *et al,* 1994]. Significant changes were observed in the chemical shifts of H2, H6, H9, H5′ and H8′ protons when cinchonidine and pyruvate (methyl and ethyl) were combined (Figure 4.8).

The NMR studies also support the idea of π-π communication between conjugated double bonds of the aromatic rings of cinchonidine. Figure 4.9a shows the chemical shift of H5′ and H8′ proton, where it is observed that H8′ proton goes to downfield and H5′ proton goes to upfield. Proton H9 also shows a downfield shift, Figure 4.9b. This chemical shift of proton (H9) shows interaction between the OH group of cinchonidine and the O atom of pyruvate. H2 and H6 proton goes to downfield due to the hydrogen bonding between the adsorbed cinchonidine modifier quinuclidine N and O atoms of the methyl pyruvate (Figure 4.9c). Thus, the overall NMR study suggests that besides aliphatic part of cinchonidine, the aromatic ring (quinoline) is also involved in the formation of the pyruvate-cinchonidine interaction via π-π electrons [Baiker 2000]. The later interaction (quinuclidine N and O atoms of pyruvate) is stronger than the π-π interaction mentioned above; however, the π-π interaction might be sufficient to alter the chemical shift recorded in NMR with time (Table 4.8). Both type of interactions help to control

the mode of adsorption of the substrate and chiral induction. Thus, cinchonidine behaves like a bidentated ligand and forms a substrate-modifier complex. NMR study elucidated the 1:1 substrate modifier complex [Bartók and Felföldi *et al,* 1998].

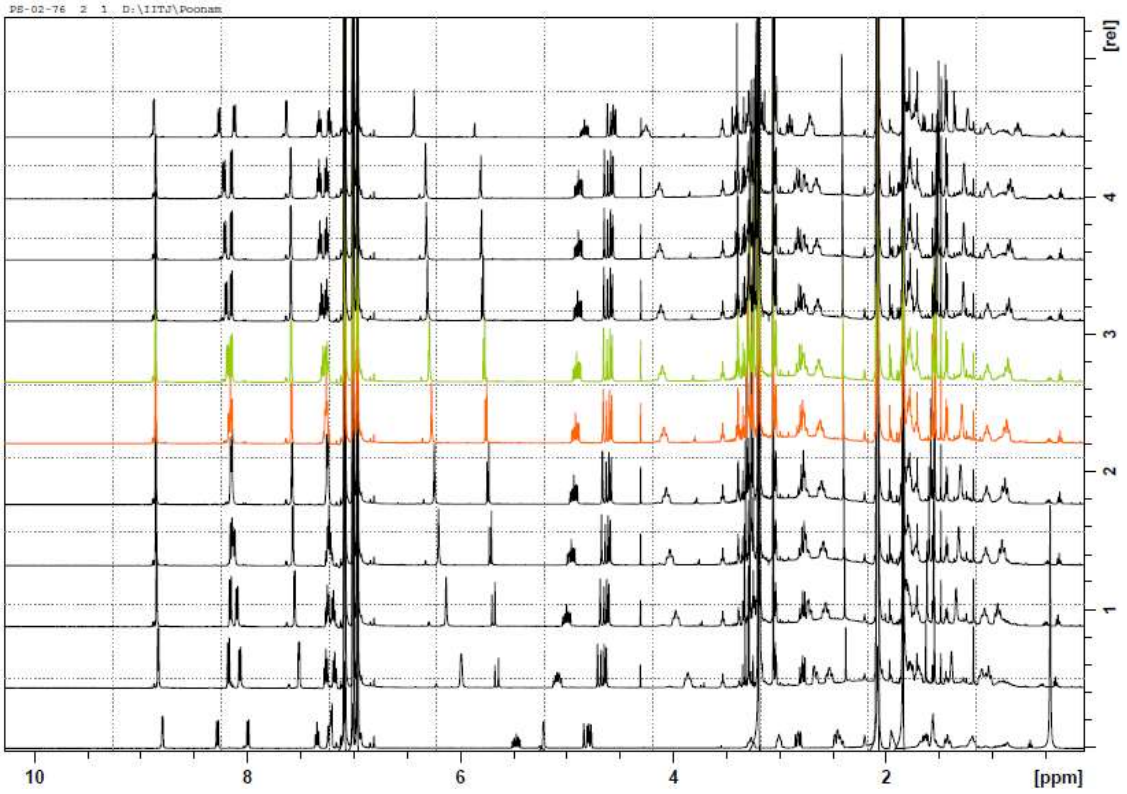


Figure 4.8 A time depend ^{1}H NMR studies of interaction between cinchonidine and methyl pyruvate

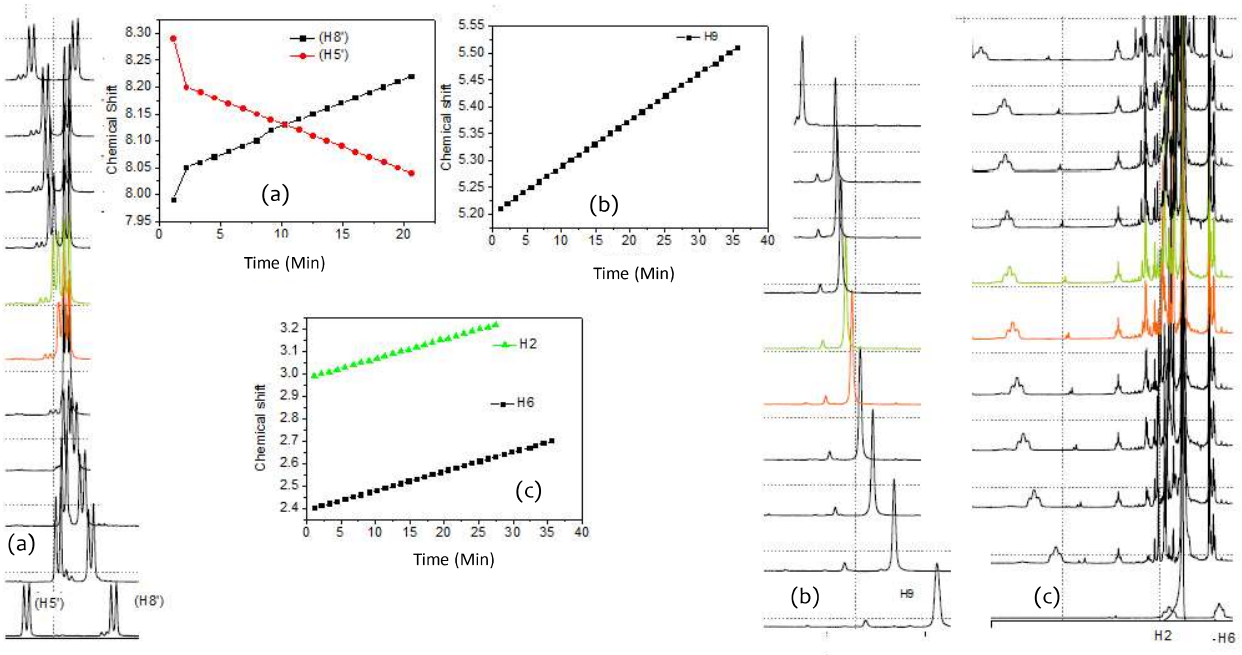


Figure 4.9 NMR spectra of (a) H5' and H8' protons and corresponding plot of chemical shift versus reaction time, (b) NMR spectra for H9 proton and corresponding plot of chemical shift versus reaction time, (c) NMR spectra of H2 and H6 proton and corresponding plot of chemical shift versus reaction time

Table 4.8 Chemical shift during interaction of cinchonidine and pyruvate

Proton	Cinchona (Cinchonidine/cinchonine)	Cinchonidine + Pyruvate
H2'	8.79	8.87
H3'	7.20	7.62
H5'	8.27	8.11
H6'	7.24	7.31
H7'	7.33	7.24
H8'	7.98	8.25
H6AX	2.40	2.68
H6EQ	2.20	2.20
H5AX	1.61	1.78
H5EQ	1.56	1.42
H4	1.61	1.49
H3	2.11	1.81
H2AX	2.99	3.04
H2EQ	3.24	4.22
H7AX	0.854	0.74
H7EQ	0.633	0.34
H8	2.808	2.88
H9	5.21	5.87

After studying the interaction substrate-modifier, it was found that there are some factors which can affect the enantioselectivity of asymmetric hydrogenation reaction.

In case of the asymmetric hydrogenation reaction of pyruvate the enantioselectivity affecting factors are:

1. Change in Quinoline Moiety

It was found that the quinoline moiety of cinchona helps in absorption of the catalyst on the surface and it also interacts with substrate by a π-π interaction [Blaser and Jalett *et al,* 1997]. It suggests that the planarity of quinoline ring plays an important role in absorption. If quinoline moiety gets hydrogenated during the reaction, then there is a lack in planarity of the ring and it causes a loss in absorption. It is a possible explanation for the decrease in the rate of reaction and enantioselectivity.

2. Effect of Changes in Quinuclidine Moiety

During the asymmetric hydrogenation reaction, the role of quinuclidine nitrogen is to bond with a substrate and in chirality transfer. If any processes do the alkylation of quinuclidine nitrogen then cinchona losses its modifier property.

3. Effect on Enantioselectivity due to Structure Change in Modifier

It was reported that cinchonidine and quinine always give preferentially (R)-products [Blaser and Jalett *et al,* 1997, Bartók and Sutyinszki *et al,* 2005], while cinchonine and quinidine led to an excess of (S)-products [Bartók and Sutyinszki *et al,* 2003]. The absolute configuration of C8 or C9 controls the selectivity of the product [Blaser and Jalett *et al,* 1991]. The relative position of any group (alkyl and aryl) on quinoline ring has a strong effect on the magnitude of the enantiomeric excess and reaction rate. The 10, 11-dihydro derivatives in the cinchonidine series give slightly higher enantioselectivity, whereas the effect for the cinchonine series is ambiguous.

4. Solvent Effect

During the experiment, a significant solvent effect on the magnitude of the enantioselectivity and on the rate of the modified catalytic system was observed [Collier *et al,* 1998]. In most cases, the acetic acid gave the best ee values, compared to ethanol or toluene. It means that if acetic acid is used as solvent, then less amount of modifier was needed. For getting the same enantioselectivity in ethanol and toluene, more amount of modifier concentration was required.

4.5.2 Possible Interaction Model of Ethyl 2-oxo-4-phenylbutanoate, Pt and Chiral Polyamide in Asymmetric Hydrogenation Reaction

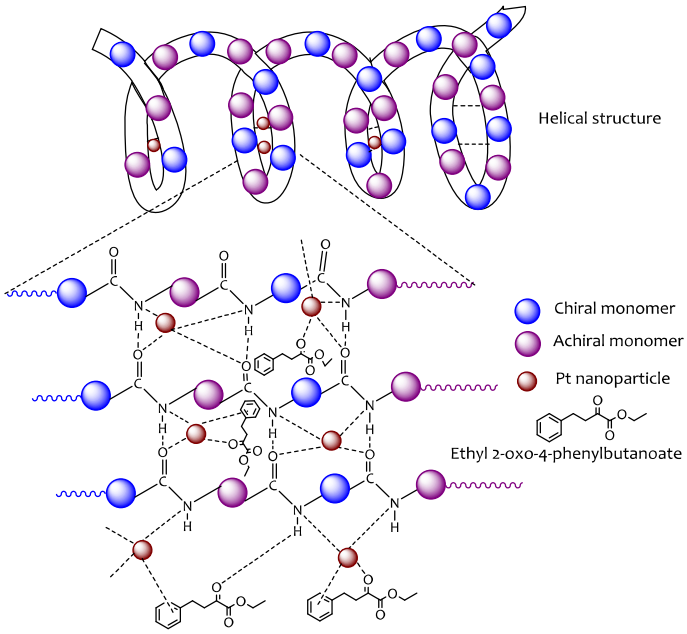


Figure 4.10 Possible interactions between Pt, chiral polyamide and substrate

This study proposes a possible model of interaction between Pt, ethyl 2-oxo-4-phenylbutanoate and chiral polyamide (Figure 4.10**)**. The interaction between the chiral polyamide and Pt is explained by HRTEM. To study the interaction of Pt on the chiral polyamide surface, various Pt/Chiral polyamides catalysts (I-IV) were synthesized and characterized in Chapter 3, by varying methylene bridge of diamine monomer which led to

change the distribution of platinum particles, due to amide–platinum interaction. It was observed in HRTEM images that inter-particle distance was proportional to the number of carbon atoms between two amide groups, where average inter-particle distances were 0.71, 1.41 and 2.77 nm in catalyst I, IV and V, respectively (Figure 4.11). The Pt nanoparticles were well dispersed at a particular distance on chiral polyamide. It was observed that the distance between nanoparticles increased with number of carbon atoms between two amino groups of diamine. These isolated particles may behave like single atoms with 0.23 nm interplanar distances Figure 4.11 (inset). In polyamides, consecutive amide groups have different conformations and the presence of non-covalent bonds, such as hydrogen bonding and π−π stacking constructs helical conformation as observed in CD spectra, contribute significantly to the transfer of chirality (Poly 1-5, Chapter 3, Table 3.5) [Fernandez-Santin *et al,* 1987, Chen *et al,* 2013, Raynal *et al,* 2013].

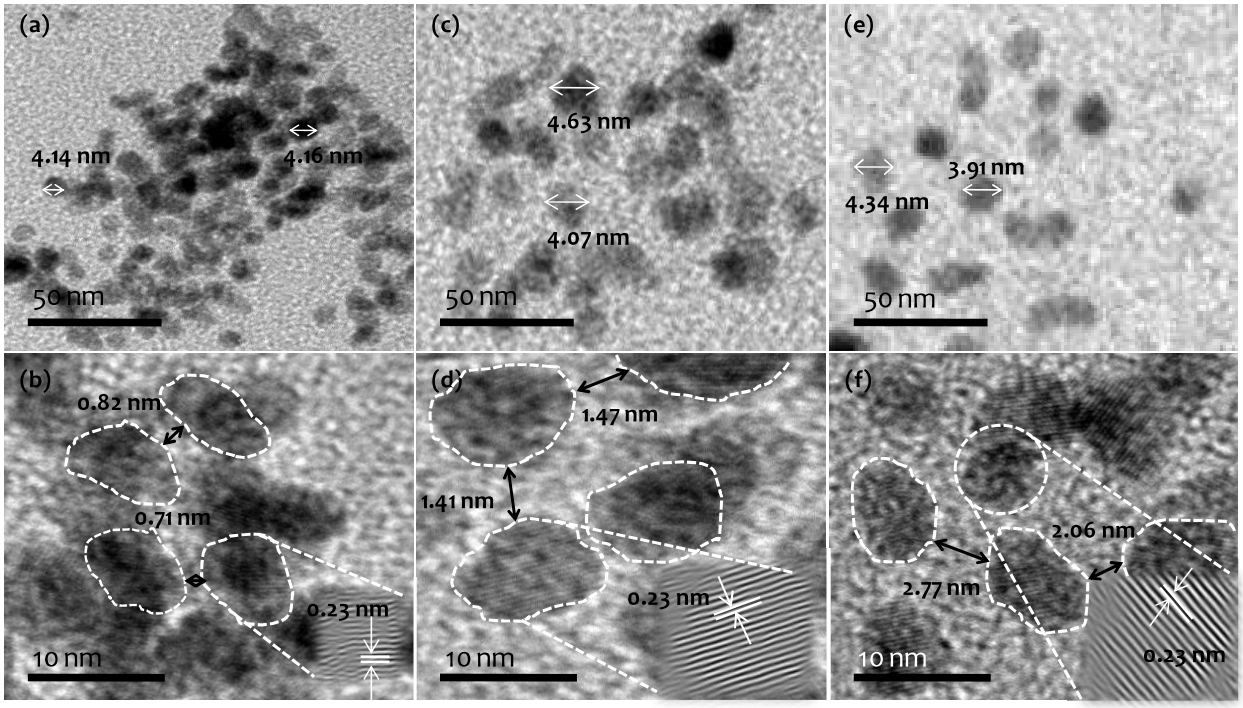


Figure 4.11 HRTEM images of (a, b) Catalyst l, (c, d) Catalyst lll, and (e, f) Catalyst V

4.6 MECHANISM OF HYDROGENATION REACTION

The fundamental aim of heterogeneous catalysis research is to understand mechanisms [Horiuti and Polanyi 1934, Blaser 1991, Gallezot 2002] at the molecular level, and then to design and synthesize catalysts with desired active sites. Heterogeneous catalysis occurs when the reactant, chiral modifier and hydrogen molecules are adsorbed on the surface of the catalyst. For understanding the mechanism of the hydrogenation reaction, a representative example of Pt loaded carbon nanotube catalyst was used (Figure 4.12).

In this process, the hydrogenation molecule, substrate and chiral molecule are absorbed on Pt surface via some interaction. Further, physisorption happens followed by chemisorptions in which substrate is absorbed via π-π interaction between carbonyl group of α-ketoester and Pt. Chiral modifier is absorbed on the surface of Pt by quinoline ring via π-π communication. On the surface of Pt, substrate and modifier come into contact and make an interaction that helps in selectivity of the product. At the same time, hydrogenation molecules start to transfer to the substrate and form a product. After reaction completion, the product desorbs from the catalyst surface.

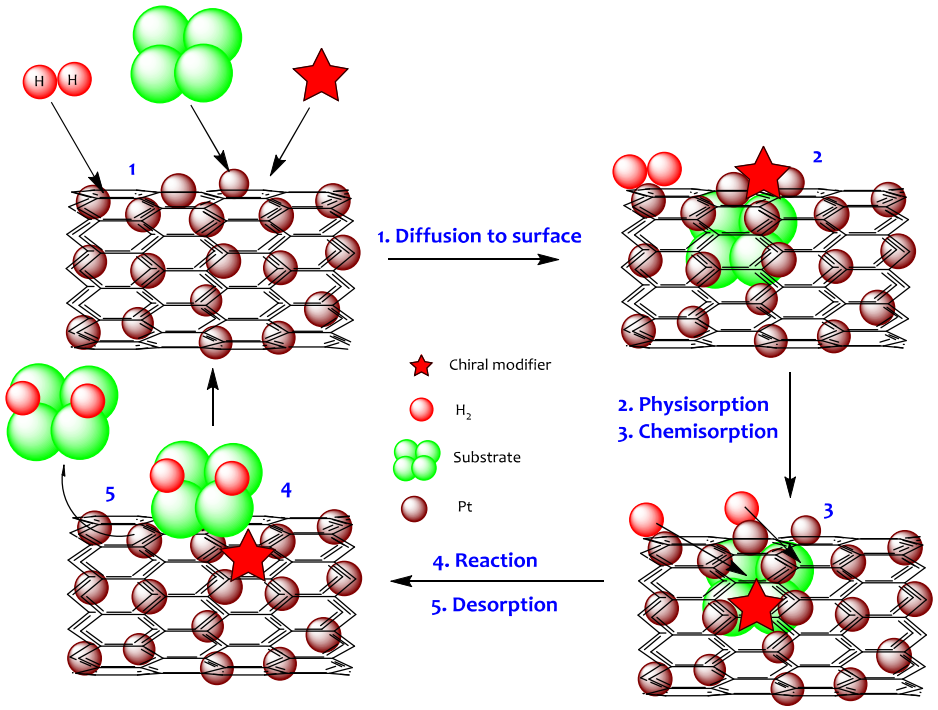


Figure 4.12 Mechanism of asymmetric hydrogenation reaction

4.7 RECYCLABILITY OF CATALYSTS

Heterogeneous catalysts are more stable, which increases their importance in organic synthesis [Morawsky and Prüsse *et al,* 2000]. The stability and recyclability performance of catalysts were tested at 10 fold substrate scale under optimized reaction conditions. The catalyst was highly recyclable with relatively constant conversion and enantioselectivity. Different characterization of recycled catalysts after ten cycles revealed individuality of catalytic reaction centre, that is, secured high enantioselectivity. Thus, these catalysts were recoverable and reusable without significant loss of activity

4.8 CONCLUSION

In conclusion, asymmetric heterogeneous hydrogenation of methyl pyruvate is a representative example of α-ketoester which was studied using Pt/C as a catalyst. Pt/MWCNTs were the most efficient catalyst and provided highest enantioselectivity. The supremacy of Pt/MWCNTs is attributed to the high absorption of cinchonidine/substrate on atomically dispersed Pt nanoparticles loaded on nanochannels of MWCNTs which maximizes metal utilization. Pt hexagonal nanocrystals loaded carbon materials were showed excellent activity in asymmetric hydrogenation reaction and higher activity of Pt (111) surface. It was found that the shape-controlled NCs represent a new frontier in heterogeneous catalysis of α-ketoesters. Out of various α-ketoesters, methyl pyruvate gives 99.9% enantioselectivity in case of Pt HNC loaded carbon nanotubes due to the high dispersion of Pt on the high surface area of nanotubes. Significant shifts in NMR spectrum were observed due to 1:1 substrate-modifier interaction. Pt nanopaticles loaded chiral polyamide catalyst proved to be a highly active catalyst for asymmetric hydrogenation of industrially important ketoesters, like ethyl 2-oxo-4-phenylbutanoate, under solvent free conditions. In this specific case, chirality was introduced from the support. The present study establishes a relation between enantioselectivity and dispersion of Pt nanoparticles on chiral polyamide. The dispersion was high in case of distant amide groups containing polyamide, leading to highly isolated platinum nanoparticles that behave like single atom catalysts, which allow to excellent conversion and enantioselectivity. The catalyst reusability was tested up to ten cycles without any significant drop in selectivity.