

2011

Amino Acids Functionalized Heterogeneous Chiral Catalyst

Hadi Nur, *University Technology Malaysia*

Lim Kheng Wei, *University Technology Malaysia*

AMINO ACIDS FUNCTIONALIZED HETEROGENEOUS CHIRAL CATALYST

RESEARCH MONOGRAPH

Prof. Dr. Hadi Nur

Professor

Ibnu Sina Institute for Fundamental Science Studies

Universiti Teknologi Malaysia

Lim Kheng Wei

Science Officer

Ibnu Sina Institute for Fundamental Science Studies

Universiti Teknologi Malaysia

ABSTRACT

Heterogeneous asymmetric catalysis remains as an exciting research field in chiral catalysis since the heterogeneous catalyst can be separated easily from the reaction mixture compare to conventional homogeneous catalyst. The aim of the research is to develop and investigate a novel heterogeneous asymmetric catalyst using amino acid as chiral promoter. The catalysts were synthesized by attachment of amino acids such as L-glutamic acid, L-leucine and L-phenylalanine onto the hydrophilic part of hydrolyzed octadecyltrichlorosilane (OTS). The short-range order structure of silicon and organic groups in the catalysts has been confirmed by solid-state ^{29}Si and ^{13}C cross-polarization magic-angle-spinning (MAS) NMR spectroscopies, respectively. The solid state MAS NMR results showed that the amino acids interacted with hydrolyzed OTS. This phenomenon was supported by ^{13}C NMR spectra which showed the signals of the peaks of L-glutamic acid, L-leucine and L-phenylalanine were shifted towards a higher magnetic field. It was confirmed by ^{29}Si NMR spectra which showed the peaks of cross-linked $-(\text{OH})\text{Si}(\text{R})-\text{O}-(\text{OH})\text{Si}(\text{R})-$ ($\text{R}=\text{octadecyl group}$) whereas those of $\text{R}-\text{Si}\equiv(\text{OSiR})_3$ were not present in amino acid-hydrolyzed OTS. This result suggested that the amino acid was attached via cross-linked $-(\text{OH})\text{Si}(\text{R})-\text{O}-(\text{OH})\text{Si}(\text{R})-$ of hydrolyzed OTS. The amino acid-hydrolyzed OTS materials were used as catalysts for the asymmetric hydration of epoxycyclohexene to yield two diastereoisomers, namely (1*R*,2*R*)-*trans*-1,2-cyclohexanediol, (1*S*,2*S*)-*trans*-1,2-cyclohexanediol and *cis*-1,2-cyclohexanediol.

TABLE OF CONTENTS

CHAPTER	TITLE	PAGE
	ABSTRACT	i
	TABLE OF CONTENTS	ii
	LIST OF TABLES	v
	LIST OF FIGURES	vi
	LIST OF SYMBOLS	ix
I	INTRODUCTION	1
	1.1 Problem identification	1
	1.2 Stereochemistry	2
	1.3 Enantioselective Synthesis	5
	1.4 Statement of Problem	8
	1.4 Scope and Objectives of The Study	9
	1.5 Strategy of The Research	9
II	LITERATURE REVIEW	13
	2.1 Chirality and Enantioselective Chemical Processing	13
	2.2 Importance of Chirality	14
	2.3 Chiral Technologies	16
	2.3.1 Chiral Separation	17
	2.3.2 Chiral Synthesis	18
	2.3.3 Diastereomeric Crystallization Technique	19
	2.3.4 Resolving Agents	20

2.3.5	Resolution of Different Materials	20
2.3.6	Resolution of Amino Acids (Amphoteric Racemates)	21
2.3.7	Resolution of Neutral Compounds	21
2.4	Homogeneous Asymmetric Catalyst	22
2.5	Heterogeneous Asymmetric Catalyst	23
2.5.1	Modification of Metal/Solid Surfaces with Chiral Molecules	25
2.5.2	Attachment of Chiral Auxiliaries to Reactant	27
2.5.2	Intrinsically Chiral Solid/Surface Catalyst	27
2.6	Important Criteria for Enantioselective Catalysts	28
2.7	Amino Acids	29
2.7.1	Chirality of Amino Acids	30
2.7.2	The Hydropathy Index of Amino Acids	32
2.8	Octadecyltrichlorosilane	33
2.9	Determination of Enantioselectivity by Chiral Column Chromatography	34
III	EXPERIMENTAL	38
3.1	Synthesis of Heterogeneous Asymmetric Catalyst	38
3.2	Characterization of Catalyst	39
3.2.1	X-ray Diffraction (XRD) Spectroscopy	39
3.2.2	Dispersibility of Catalyst in Immiscible Organic and Aqueous Phases	40
3.2.3	Solid State Magic Angle Spinning Nucleus Magnetic Resonance	40
3.2.4	Fourier Transform Infrared	41
3.2.5	Specific Surface Area Analysis	42
3.2.6	Thermogravimetric Analysis (TGA)	43
3.3	Catalytic Performances	43

IV	RESULTS AND DISCUSSION	45
4.1	Physical Properties	45
4.2	Hydrophilicity-Hydrophobicity of Catalysts	46
4.3	Solid State Nuclear Magnetic Resonance	47
4.4	Fourier Transform Infrared	50
4.5	Thermogravimetric Analysis	59
4.7	Enantioselective Hydration of Epoxycyclohexane	60
5	CONCLUSIONS	66
	REFERENCES	68

LIST OF TABLES

TABLE NO.	TITLE	PAGE
2.1	Standard amino acids and their hydropathy indexes	33
4.1	BET surface area of OTS-Glu, OTS-Leu and OTS-PheAla	46
4.2	¹³ C chemical shift in OTS-Glu, OTS-Leu and OTS-PheAla in comparison to hydrolyzed OTS and pure amino acids	50
4.3	Reaction yields of hydration of epoxycyclohexane	61

LIST OF FIGURES

FIGURE NO.	TITLE	PAGE
1.1	The two enantiomers of limonene.	3
1.2	The Cahn – Ingold – Prelog convention	4
1.3	The two enantiomers of glyceraldehydes	5
1.4	The rotation of plane-polarised light by L and D optical isomers	4
1.5	(S)-Thalidomide	6
1.6	(R)-Salbutamol	6
1.7	(R,R,S)-Deltamethrin.	7
1.8	Attachment of chiral amino acid onto the hydrophilic part of hydrolyzed OTS.	11
1.9	The interaction of amino acid with cross-linked – (R)Si(OH)-O-(R)Si(OH)- of hydrolyzed OTS (R = octadecyl group).	12
2.1	Enantiomers of a drug that have a different therapeutic effect	15
2.2	Examples of biologically active compounds prepared from optically pure epoxides and halohydrins	16
2.3	Methods of obtaining chirally pure compounds	17
2.4	Models of heterogeneous asymmetric catalysis.	24
2.5	Schematic view and important properties of immobilized complexes	26
2.6	An amine portion and a carboxylic acid part in amino acid	30

2.7	Structural formula of amino acids	31
2.8	Structural diagrams of some amino acids	32
2.9	Chemical structure of <i>n</i> -octadecyltrichlorosilane (OTS).	34
2.10	Structure of α -, β -, or γ -cyclodextrin (6, 7, or 8 glucose units)	36
2.11	Cross section through the cone of α -, β -, or γ -cyclodextrin (6, 7, or 8 glucose units) with the hydroxyl groups outside the cavity and the ring of glycosidic oxygens -O- inside	37
3.1	Nomenclature and chemical shifts of some silyl species	41
3.2	Hydration of epoxycyclohexene to 1,2-cyclohexanediol	43
4.1	XRD patterns of OTS-Glu, OTS-Leu and OTS-PheAla	45
4.2	Dispersibility of hydrolyzed OTS-Glu in a mixture of toluene and water under stirring and static conditions	48
4.3	Photograph of w/o type of emulsion stabilized by OTS-Glu. Photograph was taken from the emulsion after 2 h under stirring condition	49
4.4	^{13}C CP/MAS NMR of hydrolyzed OTS, L-glutamic acid (Glu) and OTS-Glu	51
4.5	^{13}C CP/MAS NMR of hydrolyzed OTS, L-leucine (Leu) and OTS-Leu	52
4.6	^{13}C CP/MAS NMR of hydrolyzed OTS, L-phenylalanine (PheAla) and OTS-PheAla	53
4.7	^{29}Si NMR of (a) hydrolyzed OTS and (b) OTS-Leu	54

4.8	FTIR spectra of L-glutamic acid, OTS-Glu and hydrolyzed OTS	56
4.9	FTIR spectra of L-leucine, OTS-Leu and hydrolyzed OTS	57
4.10	FTIR spectra of L-PhenylAlanine, OTS-PheAla and hydrolyzed OTS	58
4.11	Thermograms (TGA) of water absorption on OTS-amino acids	59
4.12	Relationship between hydrophaty index and percentage of adsorbed water of OTS-amino acids.	60
4.13	Enantioselectivity of hydration of epoxycyclohexane by hydrolyzed OTS-amino acids	62
4.14	Gas chromatograms of (a) (1 <i>R</i> ,2 <i>R</i>)- <i>trans</i> -1,2-cyclohexanediol, (b) (1 <i>S</i> ,2 <i>S</i>)- <i>trans</i> -1,2-cyclohexanediol and (c) (1 <i>R</i> ,2 <i>R</i>)- <i>trans</i> -1,2-cyclohexanediol and (1 <i>S</i> ,2 <i>S</i>)- <i>trans</i> -1,2-cyclohexanediol after hydration of epoxycyclohexane by using OTS-Glu as a catalyst	63
4.15	Hydrophilicity effects on enantioselectivity	64
4.16	Amphiphilic chiral solid catalyst as heterogeneous micellar catalyst in enantioselective hydration of epoxycyclohexene	65

LIST OF SYMBOLS AND ABBREVIATIONS

OTS	-	Octadecyltrichlorosilane
FTIR	-	Fourier Transform Infrared
TGA	-	Thermogravimetric Analysis
MAS NMR	-	Magic Angle Spinning Nuclear Magnetic Resonance
KBr	-	Potassium Bromide
TMS	-	Tetramethylsilane
MHz	-	Mega Hertz
ppm	-	Part Per Million
e.e.	-	Enantiomeric Excess

CHAPTER I

INTRODUCTION

1.1 Problem Identification

As evidenced by the numerous publications in the field of heterogeneous asymmetric catalysis, over the years a large number of variously immobilized chiral catalysts have been developed for a broad range of enantioselective reactions. Although some of these catalysts have demonstrated excellent performances in terms of activity, enantioselectivity, stability and/or reusability, the number of recognized industrial processes that use heterogeneous enantioselective catalysts for the commercial production of chiral compounds remains extremely small. None of the immobilized chiral metal complexes has been applied industrially for large - scale production, despite several types of immobilized catalysts having demonstrated good potential for technical applications [1-4]. Clearly, with few exceptions, most of the heterogeneous catalytic asymmetric methodologies developed to date have not been sufficiently mature to compete with alternative industrial methods (e.g. homogeneous catalysis, racemic mixture resolution).

Nevertheless, one believes that heterogeneous asymmetric catalysis is an important field in the future, in view of its undisputable advantages over homogeneous counterparts with regards to separation and economy. To date, chemists have developed, with varying degrees of success, a wide variety of heterogenization techniques which will steadily broaden their applicability in the future. Finally, the identification of more economic and reliable heterogeneous asymmetric catalytic systems with high activity, selectivity, stability and reusability

remains a challenging, but very worthwhile, goal which calls for collaborative efforts from both industry and academia [5-6].

The control of enantioselectivity by heterogeneous asymmetric catalysis remains a big challenge today. The main drive has been to find new, exciting routes to chiral molecules while achieving high enantiomer selectivity. The demand for chiral compounds, often as single enantiomers, has escalated sharply in recent years, driven particularly by the demands of the pharmaceutical industry, but also by other applications, including agricultural chemicals, flavors, fragrances, and materials. Two-thirds of prescription drugs are chiral, with the majority of new chiral drugs being single enantiomers. Although the most obvious applications are bio-related, materials science also relies on the properties imparted by chirality, notably in chiral polymers and liquid crystals. This widespread demand for chiral compounds has stimulated intensive research to develop improved methods for synthesizing such compounds.

1.2 Stereochemistry

The origin of homochirality, that is the preference of one-handed form of biological molecules has puzzled scientists since the chiral nature of molecules was discovered by Pasteur [7, 8] more than 150 years ago. On a molecular-level, homochirality represents an intrinsic property of the building blocks of life. Although most amino acids can exist in both left- and right-handed forms, life on earth is made of left-handed amino acids, almost exclusively. Similarly, many other biochemically vital molecules are handed: DNA is right-handed, and so are all the sugars we can use.

Chirality is a geometrical property. A molecule is said to be chiral if its mirror image can not be superimposed on itself. On the other hand an achiral molecule can be superimposed on its mirror image. Chiral molecules obviously contain chiral centres but these centres are better referred to as asymmetric or better still, stereogenic centers.

A common type of chiral molecule is one that contains a tetrahedral carbon atom attached to four different groups. The carbon atom is the asymmetric centre of the molecule. Such molecules exist as non-superimposable mirror images of each other and are stereoisomers. Such stereoisomers are called enantiomers. Enantiomers are said to be chiral (from the Greek word $\chi\epsilon\iota\rho$ for hand), meaning that they are non-superimposable mirror images of each other, like a left and right hand. They have identical physical properties such as boiling and melting point and share the same chemical reactivity patterns in an achiral environment. An example of a pair of enantiomers is limonene. The (R)-enantiomer has an orange flavour present and the (S)-enantiomer has a lemon flavour. This is shown in Figure 1.1.

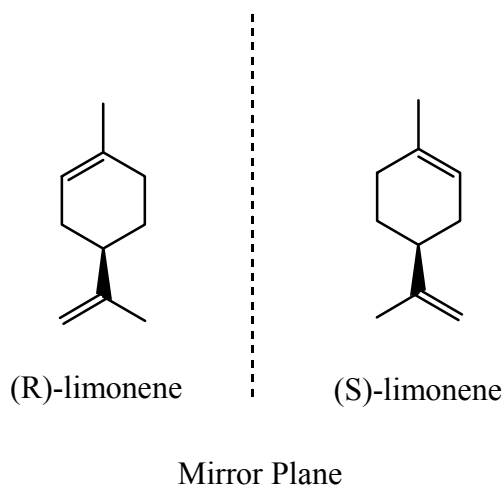


Figure 1.1: The two enantiomers of limonene.

The term (R) or (S) refers to the absolute configuration of the enantiomers. This is the configuration about the central chiral carbon centre. The (R) and (S) notation is called the Cahn-Ingold-Prelog system [9, 10] and is determined by orientating the asymmetric carbon centre and then the group with the lowest molecular weight is placed farthest away from the eyes of the viewer. The remaining three groups are then placed in order of decreasing priority. If the sequence is turning clockwise then the enantiomer is said to be the (R) one. If the circle goes anti-clockwise then the enantiomer is the (S) one. This is shown in Figure 1.2.



Figure 1.2: The Cahn – Ingold – Prelog convention [2, 3].

An example of such enantiomers is glyceraldehyde and is shown in Figure 1.3.



Figure 1.3: The two enantiomers of glyceraldehyde.

The absolute configuration is one of two ways of distinguishing between enantiomers and is the best way because it gives information about the spatial arrangement of the substituents around the stereogenic centre of the molecule.

The other way of distinguishing between enantiomers is by optical rotation due to a specific distinguishing physical property of two stereoisomers to be able to rotate plane polarised light in opposite directions. Normal light consists of electric and magnetic fields oscillating in all directions perpendicular to each other and to the direction in which the light travels. In plane-polarised light the component electric and magnetic fields are contained within two perpendicular planes. When plane polarised light is passed through a symmetric molecule, every encounter of light with the mirror-image molecule orientation is matched by an encounter with the mirror-image molecular orientation, resulting in a net zero rotation of light. The degree (angle) of rotation is easily measured using a polarimeter and has a specific value for each optically active substance. If the rotation is to the right (clockwise) the substance is dextrorotatory; if the rotation is to the left (counterclockwise) it is levorotatory. The symbols (+) or (d) are used to denote dextrorotatory and (-) or (l) to

denote levorotatory. This is shown in Figure 1.4. Distinguishing enantiomers by their optical rotation clearly does not give any structural information about the molecule, which is why the absolute configuration is the preferred method.

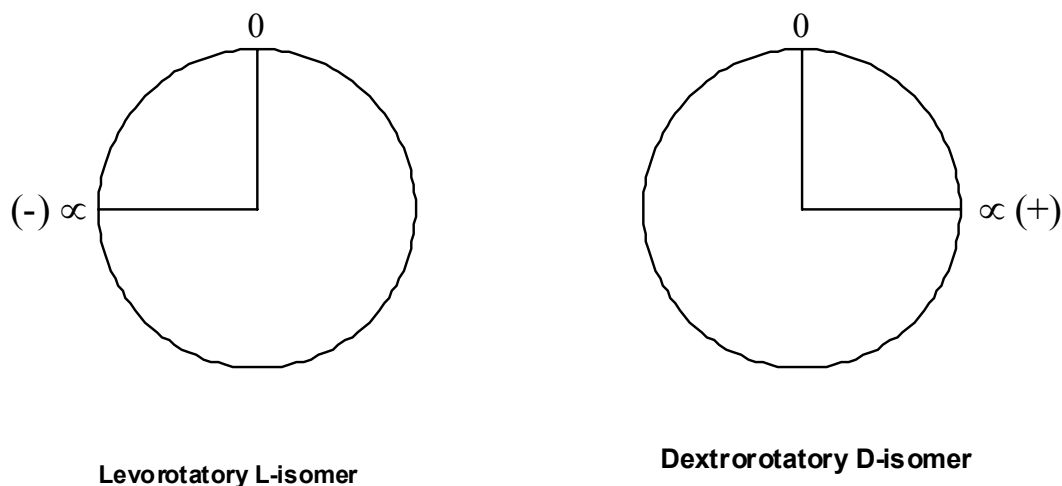


Figure 1.4: The rotation of plane-polarised light by L and D optical isomers.

1.3 Enantioselective Synthesis

The synthesis of pure enantiomers is very important for the pharmaceutical and chemical industries since even ppm levels of the undesired enantiomer can have disastrous consequences [11]. There are many examples of opposite enantiomers which give different physiological or chemical effects. Limonene is a natural example that has already been mentioned but whose effects simply change its taste. Limonene is used in many citrus cleaners and detergents and is very effective.

In fact, very often only one enantiomer exhibits a specific therapeutic action, whereas the other has to be considered as ballast, contributing to side effects, displaying toxicity, or acting as antagonist [12-15]. Despite this knowledge on the different physiological effects of enantiomers, chiral medicines have been commonly produced for a long time as equimolar mixtures of enantiomers, or racemates. The arguments for this practice were mainly technical and economical, since the

development of efficient routes to enantiopure compounds was perceived as cumbersome and expensive. However, following the understanding that different enantiomers may have qualitatively distinct physiological effects, [16-20] and instigated by stricter regulations from health authorities, a growing number of new drugs are now marketed as single enantiomers [21-23].

The thalidomide tragedy of the 1960's is commonly used as an example. It is an anti-emetic drug that was prescribed to pregnant women to help combat morning sickness and to others as a sleeping aid. It was responsible for more than 15,000 damaged fetuses and consequently resulted in babies being born with distorted limbs. The (R) enantiomer is the hypnotic drug but the (S) enantiomer is a teratogen and is responsible for the birth defects. Thalidomide was consequently banned for its intended use but it has been found to be effective elsewhere and in 2001, new clinical trials were begun of a 50/50 mixture of both the (R) and (S) enantiomers under the new name of Thalomid®, the registered name of Celgene and Pharmacia companies [24]. Thalidomide reduces growth of blood vessels and it has been tested on cancer patients, as tumours require new blood vessels. It has been used to treat weight loss associated with AIDS/HIV and on Chron's disease patients. It has also been studied for its potential property of stopping HIV progression. In fact as early as 1965, an Israeli doctor began treating leprosy patients with thalidomide with successful results.

Recently it has been found that thalidomide racemises in the body [24] so however pure the (R) enantiomer is administered, the teratogenic effects would still have occurred. The (S) enantiomer is shown in Figure 1.5.

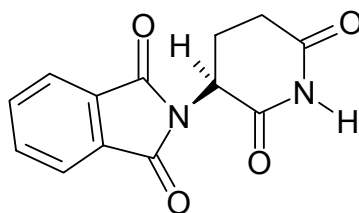


Figure 1.5: (S)-Thalidomide.

Salbutamol is used as an asthma drug and is administered in the (R) enantiomer form as this causes muscle relaxation. (S)-Salbutamol causes muscle contraction and is now thought to be the main cause of bronchial hyper responsiveness in the treatment of asthma with racemic Salbutamol. (R)-Salbutamol is shown in Figure 1.6.

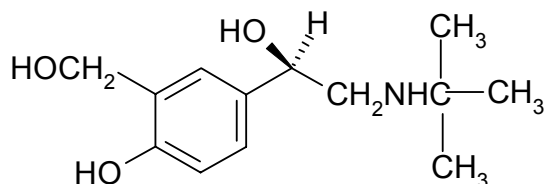


Figure 1.6: (R)-Salbutamol.

(R,R,S)-Deltamethrin is a potent insecticide whereas the (S,S,R) enantiomer is inactive. Use of the (R,R,S) enantiomer rather than a racemic mixture halves the amount that needs to be applied thereby reducing waste. Whether or not this reduces pollution is arguable, as the use of any insecticide may be harmful to the environment. (R,R,S)-Deltamethrin is shown in Figure 1.7.

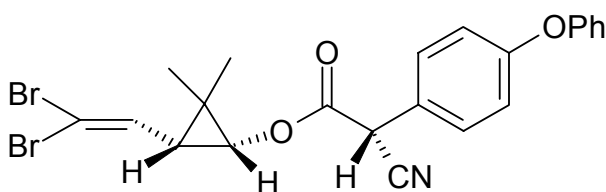


Figure 1.7: (R,R,S)-Deltamethrin.

So it can be seen that for any new drug it is important that it can be synthesized in a homochiral form if it is to be approved. The case of Thalidomide is a special one and the fact that it racemises in the body makes it an exception to this rule.

Asymmetric synthesis is the production of a preferred enantiomer from a *prochiral* substrate. The term prochiral refers to a compound or group that has an atom C-linked to two identical ligands and to two different ligands (C *aabc*). It is

prochiral because if one of the ligands a is replaced by a ligand d different from a, b and c , a chiral (asymmetric) centre is produced in $(C\ abcd)$. In other words, it is a compound or group that has two enantiotopic atoms, faces or groups. For example, CH_2XY has two enantiotopic H atoms. Asymmetric synthesis is only possible when the starting materials or conditions are optically active [25, 26]. Optically active materials cannot be created from inactive starting materials and conditions.

Optical yield or enantiomeric excess ($e.e.$) measures the efficiency of an asymmetric reaction:

$$\% (e.e.) = \{([R] - [S]) / ([R] + [S])\} \times 100$$

The importance of this field of research was underlined by the Nobel Prize in Chemistry in 2001 awarded to Knowles, Noyori and Sharpless for their work on chirally catalyzed hydrogenation and oxidation reactions.

1.3 Statement of Problem

It has been generally known that all the amino acids are chiral, with the exception of glycine. Because of their chirality, in this research, the amino acids are used in the synthesis of heterogeneous asymmetric catalysts where the amino acids act as chiral promoters. Amino acids have hydrophilic characters and many kinds of them dissolved easily in water. These properties are important and used in the designing heterogeneous asymmetric catalyst. In this research, amino acids will be reacted with octadecyltrichlorosilane (OTS), a surfactant molecule, in order to change their properties from hydrophilic into amphiphilic. Amphiphile (from the Greek $\alpha\mu\phi\iota\varsigma$, amphis: both and $\phi\iota\lambda\acute{\iota}\alpha$, philia: love, friendship) is a term describing a chemical compound possessing both hydrophilic (water-loving) and lipophilic (fat-loving) properties. Such a compound is called amphiphilic. One considers that the OTS-amino acids obtained would self-assemble to form a micelle in the immiscible mixture of organic and aqueous phases, where the lipophilic tails of the alkylsilyl groups of OTS remain on the inside of the micelle due to unfavorable interactions.

It's expected that this catalyst system can be used in asymmetric hydration reactions with acid, whereby a portion of the hydrophilic amino acids can act as a 'chiral pool' in the reaction. Based on the above considerations, the statement of problem can be defined as follows: *Is OTS-amino acids catalyst synthesized by reacting amino acids with octadecyltrichlorosilane (OTS) potential catalyst in asymmetric hydration reaction?*

1.4 Scope and Objectives of the Study

The aim of this research is to develop a novel heterogeneous asymmetric catalyst by attachment of chiral amino acid onto the hydrophilic part of hydrolyzed octadecyltrichlorosilane (OTS). Specifically, this research will lead to the synthesis of heterogeneous asymmetric catalyst. The new catalyst designed will possess tunable activity and selectivity for enantioselective hydration of epoxycyclohexane.

The objectives of the study presented in this study are:

- To develop a new approach in the preparation of heterogeneous asymmetric catalyst using amino acid as chiral promoter..
- To characterize heterogeneous asymmetric catalyst obtained by using several spectroscopic and analytical techniques.
- To study and evaluate the performances of synthesized heterogeneous asymmetric catalyst in enantioselective hydration of epoxycyclohexane.

1.5 Strategy of the Research

Our strategy is based on the ideas that the chiral reactions could be induced by chiral amino acids and the use of heterogeneous micellar catalysis for synthetic purposes will overcome practical separation problems. In order to realize these ideas, chiral amino acid will be attached to the hydrophilic part of hydrolyzed octadecyltrichlorosilane (OTS). Amino acid such as L-glutamic acid, L-leucine and L-phenylalanine are chosen because their water-soluble properties, so that they can

be easily removed by treatment with water. One expects that the attachment of amino acid resulting chiral solid catalyst with bimodal hydrophobic-hydrophilic character (Figure 1.8).

The catalyst contains both hydrophobic and hydrophilic characters will exhibit amphiphilic character. The flexibility of the hydrophobic octadecyl groups allows the formation of micellar aggregates in the system containing immiscible organic and aqueous phases.

This new heterogeneous catalyst system will be a practical alternative to soluble acid for asymmetric hydration reactions in view of the following advantages, a) truly heterogeneous b) high catalytic activity under very mild reaction conditions, c) easy separation of the catalyst by simple filtration, d) the catalyst is easy to handle and reusable for several cycles without loss of activity, and enantioselectivity and e) The present method is simple, rapid and clean over the existing procedures.

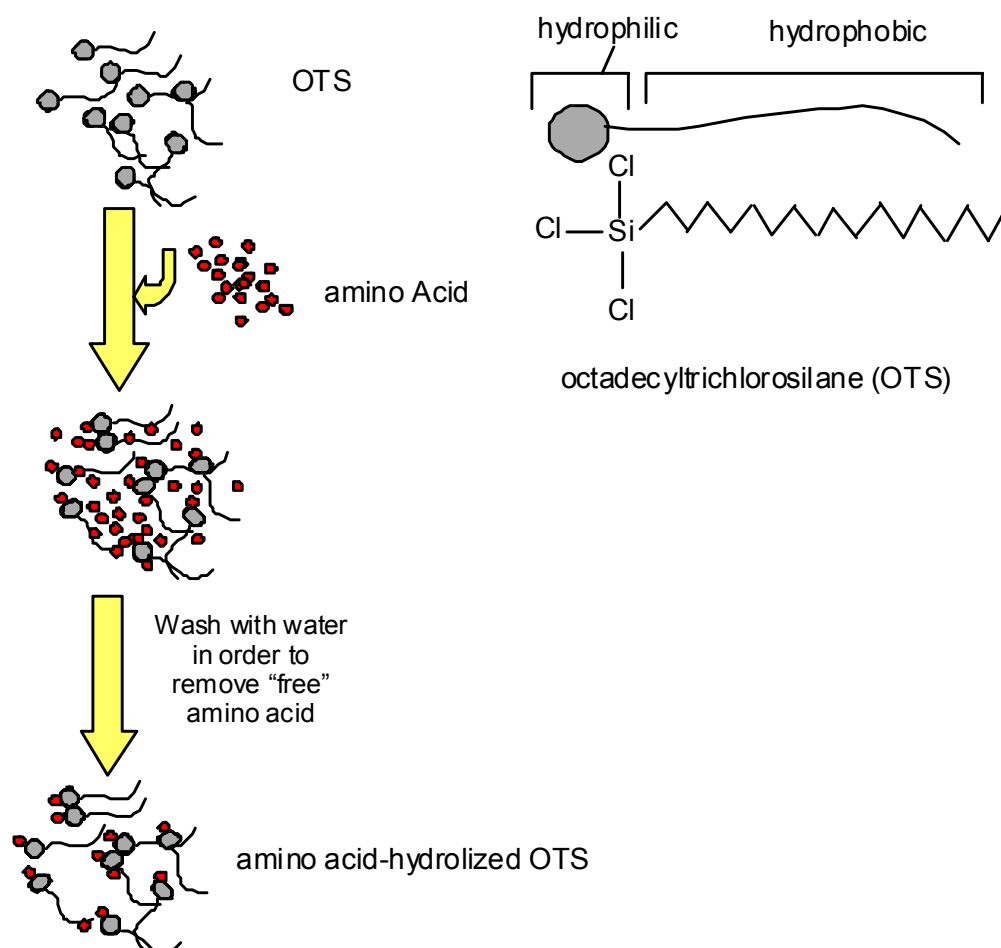


Figure 1.8: Attachment of chiral amino acid onto the hydrophilic part of hydrolyzed OTS.

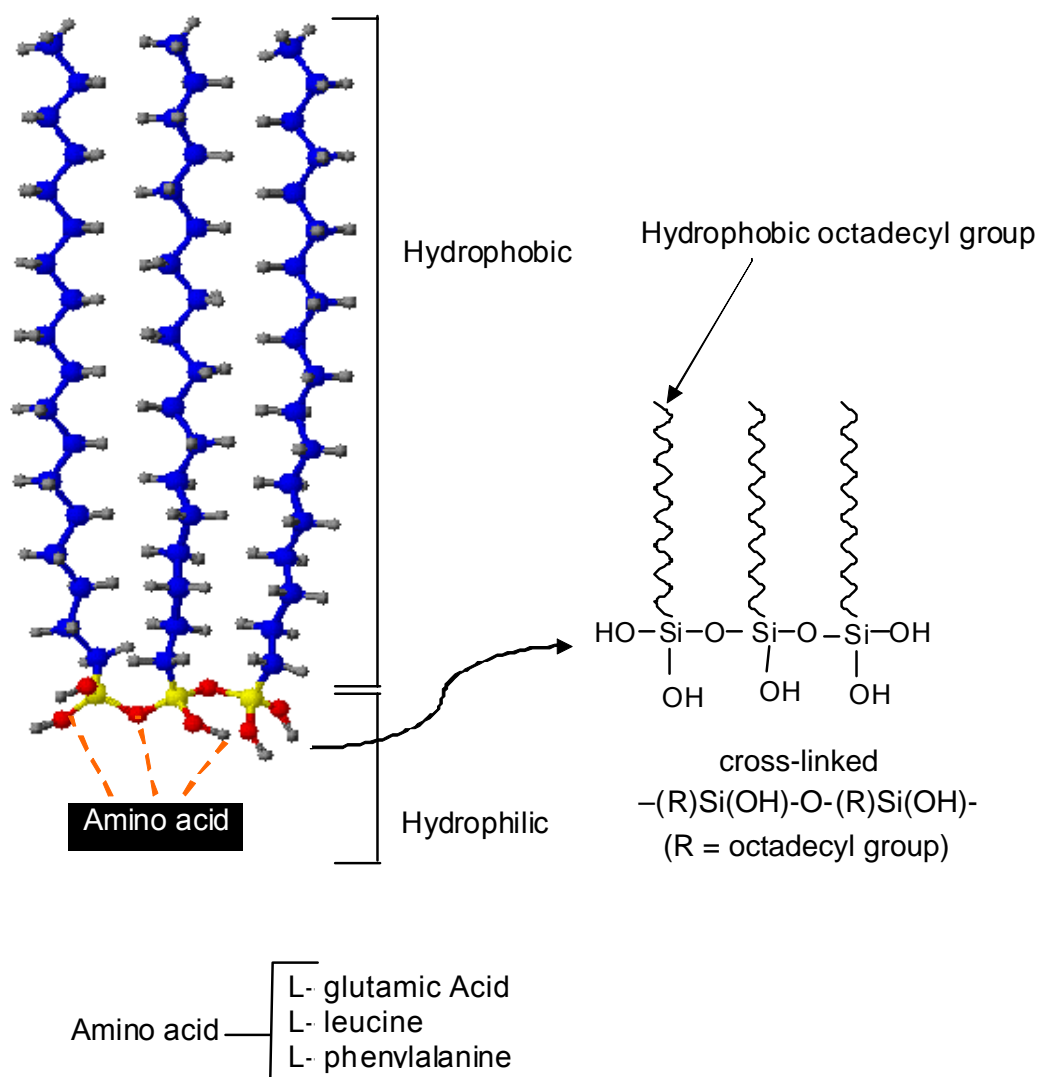


Figure 1.9: The interaction of amino acid with cross-linked $-(R)Si(OH)-O-(R)Si(OH)-$ of hydrolyzed OTS (R = octadecyl group).

CHAPTER II

LITERATURE REVIEW

2.1 Chirality and Enantioselective Chemical Processing

Chirality is a property of objects and fields that can exist at all length scales [27]. A simple manifestation of chirality is as a geometric property of objects that are nonsuperimposable on their mirror images. These exist as nonsuperimposable enantiomers of one another. From the chemist's perspective, interest arises from the fact that all biologically important molecules are chiral and exist in nature only as one of these two possible enantiomers. Such molecules include amino acids, proteins, sugars, and DNA: the building blocks of life. The origins of the homochirality of life on Earth are unknown, but the consequences are significant. The two enantiomers of chiral compounds ingested into the human body have vastly different physiological impacts, simply because they have different chemical interactions with the homochiral biomolecules of living organisms. Thus, in order to produce enantiomerically pure bioactive molecules, such as pharmaceuticals and agrochemicals, chemical processes must be devised that are enantioselective.

Enantioselective chemical processing requires the development of chiral media. Given the important role that surfaces play in many chemical processes (adsorption, catalysis, crystallization, and so forth), there is ample reason to develop chiral surfaces and an understanding of their enantioselectivity. Perhaps the earliest chiral surfaces of practical significance were the chiral stationary phases developed for chiral chromatography [27]. Another area of significant interest and activity is

that of enantioselective heterogeneous catalysis. Several such catalysts are known, but the origin of their enantioselectivity is still the subject of study [27].

2.2 Importance of Chirality

Epoxides are versatile building blocks in synthetic organic chemistry [28]. As a result of the ring strain, their susceptibility towards nucleophiles, oxidizing and reducing agents makes them versatile intermediates for the preparation of various complex molecules. An epoxide ring can be opened by a nucleophile yielding the corresponding substituted alcohol. Generally, a base-catalysed ring opening will take place at the least hindered carbon atom whereas an acid-catalysed ring opening occurs at the more substituted carbon atom. Their high reactivity and directable regioselectivity makes epoxides valuable starting compounds for the preparation of biologically active compounds.

Many biologically active compounds such as drugs are chiral, which means that they can exist in two forms called enantiomers, which are non-superimposable mirror images of each other. Since many drugs are chiral compounds and interact with a chiral receptor in the body, only one of the enantiomers has the optimal therapeutic action. To avoid side effects of the unwanted enantiomer, government regulations have, over the last 15 years, increasingly demanded the use of drugs containing only the biologically active enantiomer. One example of a chiral drug in which both enantiomers have a different therapeutic effect is Darvon and Novrad (Figure 2.1). Novrad is an anti-cough agent and Darvon a painkiller.

In Figure 2.2, some examples of biologically active compounds that can be prepared from epoxides are shown. Halohydrins can be used as direct precursors for epoxides. As the complexity of synthetic target molecules increases, more selective and mild methods for preparing and converting epoxides and halohydrins are needed. Various methods are known for obtaining a single enantiomer of a chemical compound. They can be divided in three general preparation strategies: asymmetric synthesis, use of the chiral pool, and separation of the enantiomers present in a

racemic mixture. Asymmetric synthesis is the preparation of an enantiomerically pure compound, starting from a compound containing a prochiral reaction center. The chirality can be introduced by using a chiral auxiliary, by internal asymmetric induction from a nearby chiral center in the molecule, or by external asymmetric induction using a chiral catalyst. The last method is the commercially most attractive since only a catalytic amount of a chemical or biochemical catalyst is needed to obtain the optically active compound.

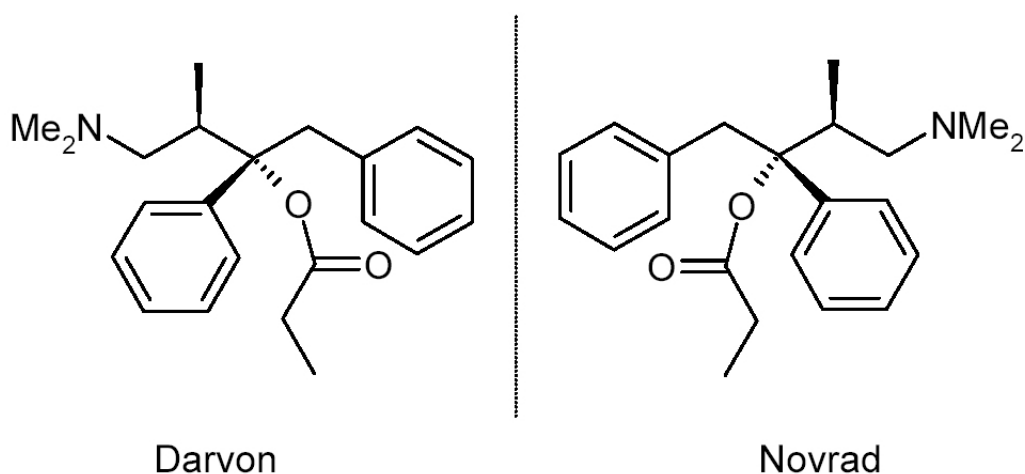


Figure 2.1: Enantiomers of a drug that have a different therapeutic effect [28].

The chiral pool consists of the optically active products present in nature, such as amino acids, organic acids, sugars, terpenes, and complex carbohydrates. An example of using the chiral pool is the anticancer drug Taxol, which can be obtained from the Pacific Yew tree *Taxus brevifolia*.¹ A total synthesis of Taxol is impractical due to the complexity of the molecule. Semi-synthetic Taxol can be obtained by using the intermediate Baccatin III which is more abundant in nature, and converting it with the use of synthetic chemistry.

The third strategy is the separation of a racemic mixture of enantiomers. One such a technique is preferential crystallisation, in which a supersaturated solution is seeded with a crystal of one enantiomer causing selective crystallisation of that

enantiomer. A second technique involves the conversion of enantiomers into diastereomers, followed again by a crystallisation. A third technique is kinetic resolution, which is based on the differences in reaction rate of the enantiomers in a racemic mixture, which can be achieved by using a chiral catalyst. If one enantiomer has been entirely converted, the reaction is stopped and the remaining enantiomer is obtained in optically pure form. A drawback to this method is that the maximum yield is only 50% of the total amount of the starting compound. Kinetic resolutions have been described using chemo-catalysts and biocatalysts.

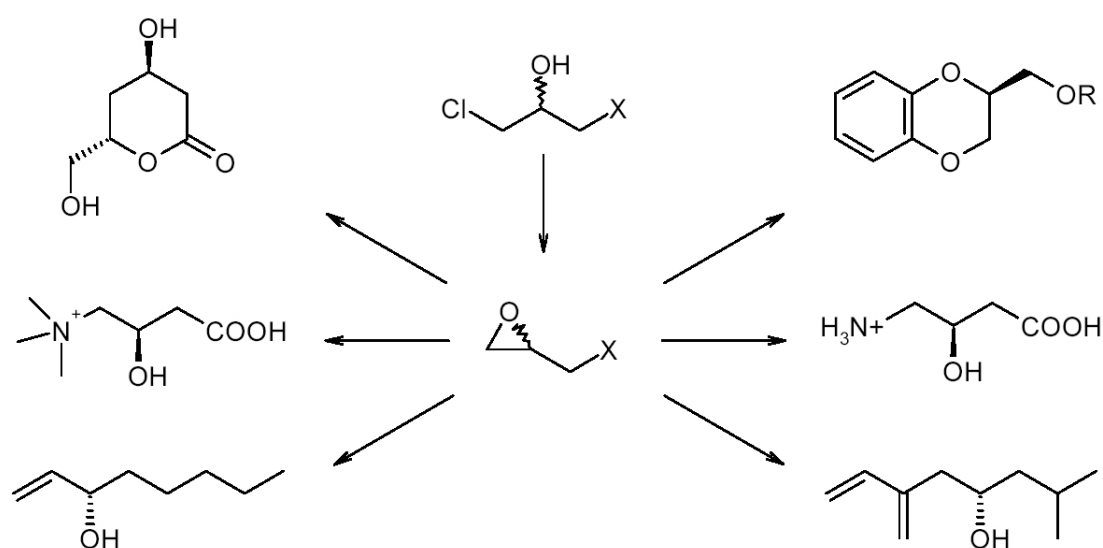


Figure 2.2: Examples of biologically active compounds prepared from optically pure epoxides and halohydrins [28].

2.3 Chiral Technologies

The niche field of chiral technologies has hugely impacted the routes to discovery and the means of production of pharmaceuticals and other chemical compounds. It is concerned with the stereoselective production and analysis of specific chiral isomers. Primarily chiral technologies fall into one of the following categories [29]:

1. Separation of enantiomers out of racemic mixtures
2. Introducing chirality in the synthetic route

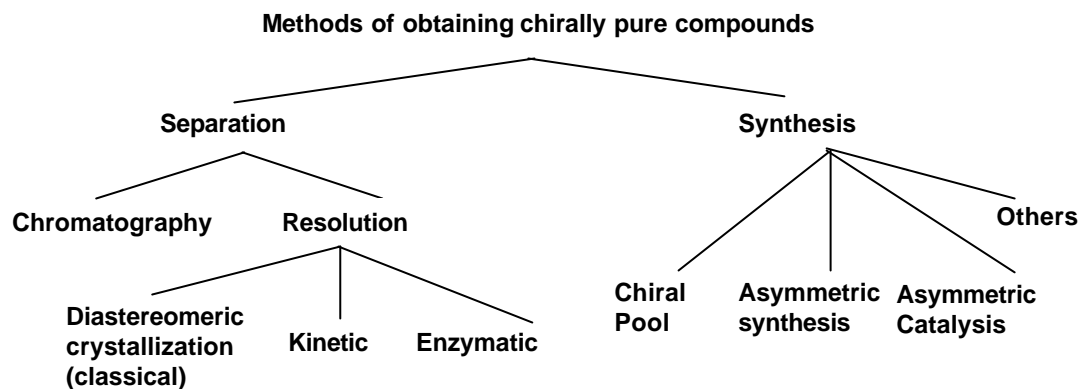


Figure 2.3: Methods of obtaining chirally pure compounds [29].

2.3.1 Chiral Separation

These techniques are used to simultaneously produce both enantiomers (to develop chiral intermediates) or to generate only one enantiomer (to develop end-use chemicals). There are two primary methods of separation [29]:

- Chromatographic separation:** This includes the use of gas chromatography (GC), supercritical fluid chromatography (SFC), capillary electrophoresis (CE) and high performance liquid chromatography (HPLC). A pair of enantiomers is considered to be resolvable if $\alpha > 1.1$. Here one enantiomer is retarded in its passage through the column because of its preferential binding to the chiral stationary phase. Because of this, the two enantiomers of a racemate emerge from the column at different times and with different volume fractions of eluent. Unfortunately, most chiral resolutions involve only small difference in eluent fractions.

b. Resolution

- **Diastereomeric crystallization:** This method chemically separates enantiomers from racemic mixture by producing a salt. This is done by adding an enantiopure acid or base to the mixture so that the resulting salts are not mirror images of each other. Instead they are diastereomers with different chemical and physical properties that allow their separation. Note that not all compounds will form complexes and therefore crystallize, but because of its easy adoption for manufacturing purposes, most companies first try this method and use the other methods only if this method does not work. Today 65% chiral products are made using the technique.
- **Kinetic resolution** which may involve selective derivatisation of one of the enantiomers in preference to the other. But they are not always possible.

2.3.2 Chiral Synthesis

The best possible way of introducing chirality in a synthetic sequence would be to use a natural product with the desired chiral characteristics [29]. However under most circumstances, this is not possible due to economic and technical reasons. The techniques for chiral synthesis have been highly complex, sophisticated and specialized; and the technology platforms developed for the purpose need to be adapted for each product. This makes the adoption of the technique for manufacturing purposes very expensive and difficult.

- **Chiral Pool:** Raw material is largely incorporated into the product. However this process needs special precautions and carefully chosen conditions and is prone to inconsistent results.
- **Asymmetric synthesis:** It involves the introduction of chirality through selective chemical transformation such as hydrogenation, oxidation, etc., have the advantage that the conversions can result in better yields with little loss of material, since the unwanted isomer is not involved. But the number of steps involved and tedious nature of those steps makes this solution very costly.

- **Asymmetric Catalysis:** This technique uses the metals known for their catalytic activities and includes the transition metals like titanium, or noble metals such as osmium, palladium, rhodium. The organic component is an enantiomeric compound, known as chiral ligand. It allows stereospecific reaction to take place and therefore avoids the formation of racemates. However, the efficiency and availability of the catalyst, the cost of the starting material and the reaction condition requirements such as very low temperature or high pressure can make this an impractical choice. Other factors to consider are the volumetric productivity and the ease of removing the catalyst.

2.3.3 Diastereomeric Crystallization Technique

Chirally-pure isomers can be obtained through a variety of techniques. The most commonly used one is the classic resolution by Diastereomeric Crystallization. Because of its easy adoption in manufacturing environment, most companies try this approach first; and use the other approaches only if this one fails. Currently, 65% of all chiral products are developed using this technique [29].

The main reasons for preferring Diastereomeric Crystallization in manufacturing are economic.

- It is easier and therefore cheaper to build up the racemate needed for Resolution methods than it is to create pure isomers using the Synthetic technologies.
- Among the resolution techniques available, Resolution by Diastereomeric Crystallization is less time and temperature sensitive and less complex
- The equipment for doing Diastereomeric Crystallization is more likely to already exist in manufacturing installations.
- Racemization in connection with Diastereomeric Crystallization ultimately produces a high yield of the enantiomer much more cheaply than the other Resolution or Synthetic procedures. (Racemization is the process of repeatedly reprocessing the “waste” portion of the resulting products; each subsequent pass yielding additional good product)

- Resolution by Diastereomeric Crystallization is also generally superior to Enzymatic Resolution in that it usually yields product of higher enantiomeric purity

2.3.4 Resolving Agents

A classical resolving agent is a chiral acid or base which has a propensity to form crystalline diastereomer when combined with racemic bases or acids. Requirements of an ideal resolving agent are:

- Proximity of stereogenic centers
- Rigid structure
- Must be a strong acid or base
- Must have chemical and optical stability
- Both enantiomers must be available and recyclable
- Must be availability in bulk quantities at low price

Amines and cinchon alkaloids in natural products typically meet these requirements and are used most often.

2.3.5 Resolution of Different Materials

For resolving carboxylic acids one usually forms salts with optically active amines. On the other hand, for resolving amine: one uses enantiopure acids like tartaric acid, malic acid and mandelic acid.

To resolve neutral compounds, one prepares covalent diastereomeric derivatives. E.g. with alcohols, one can form monophthalate, succinate or ester; while with ketones, one can form hydrazones.

2.3.6 Resolution of Amino Acids (Amphoteric Racemates)

Amphoteric racemates have both acidic and basic characteristics. E.g. in aspartic acid, there are two carboxylate groups for one amine group. The compound can be resolved as a simple acid or base. For compounds having one carboxyl and amino group each, one of the functional group must be masked.

2.3.7 Resolution of Neutral Compounds

If resolution of a neutral compound by salt formation is intended, the compound must be transformed to a derivative containing an acidic or basic group. Resolution by derivatization is typical for alcohols, aldehydes and ketones. Alcohols are almost exclusively transformed to their monophthalates or succinates. Usually phthalates (phthalic or 3-nitrophthalic anhydride) or succinic anhydride for succinates are used.

The inherent low yields of resolution can be increased to nearly 100% using various tricks. The best resolutions are those in which the undesirable enantiomer can be racemized and recycled to yields approximating 100% [29].

Chirally-pure isomers can be obtained using a variety of chiral technologies. The most commonly used is the classic resolution by Diastereomeric Crystallization. Because of its easy adoption in manufacturing environment, most companies try this approach first; and use the other approaches only if this one fails. Currently, 65% of all chiral products are developed using this technique.

The main challenge facing the companies involved in chiral research using diastereomeric crystallization is the selection of an optimum combination of resolving agents and solvents. This is a time consuming, labor intensive and error-prone process. There are hundreds of combinations to choose from and having consistent research environment is critical to the success of the research.

2.4 Homogeneous Asymmetric Catalyst

Homogeneous catalysts are generally well-defined chemical compounds or coordination complexes, which, together with the reactants, are molecularly dispersed in the reaction medium [30]. Homogeneous catalysts have a higher degree of dispersion than heterogeneous catalysts since in theory each individual atom can be catalytically active. Due to their high degree of dispersion, homogeneous catalysts exhibit a higher activity per unit mass of metal than heterogeneous catalysts. The high mobility of the molecules in the reaction mixture results in more collisions with substrate molecules. The reactants can approach the catalytically active center from any directions, and a reaction at an active center does not block the neighboring centers. This allows the use of lower catalyst concentrations and milder reaction conditions.

The most prominent feature of homogeneous transition metal catalysts are the high selectivities that can be achieved. Homogeneously catalyzed reactions are controlled mainly by kinetics and less by material transport, because diffusion of the reactants to the catalyst can occur more readily. Due to the well-defined reaction site, the mechanism of homogeneous catalysis is relatively well understood. Mechanistic investigations can readily be carried out under reaction conditions by means of spectroscopic methods. In contrast, processes occurring in heterogeneous catalysis are often obscure. The major disadvantage of homogeneous catalysts is the difficulty of separating the catalyst from the product where complicated processes such as distillation, liquid–liquid extraction, and ion exchange must often be used [31].

Homogeneous asymmetric catalysts have been developed for numerous C–H, C–C, C–O and C–N bond formation reactions, which give high enantioselection. The design has been predicated on the synthesis of chiral ligands for active catalyst centers that ensure that the desired chiral transition state is readily accessed. However, these ligands are often difficult to be recovered and reused and, for this reason, chiral homogeneous catalysts have not had the significant commercial input that researchers had initially hoped for [32]. For this reason, attention has been focused on the design of immobilized homogeneous chiral catalysts or heterogeneous chiral catalysts because these can be readily recovered by filtration for a slurry

reactor, or can be used in the numerous fixed bed reactor options available. This introduces a different aspect of catalyst usability, namely the stability of the heterogeneous catalyst, because leaching of active components can represent a real problem concerning commercialization [33].

Whilst this is particularly important for large - scale productions, unfortunately it is usually very difficult to achieve for homogeneous catalytic processes. Another major drawback often associated with homogeneous catalytic processes is that of product contamination by metal leaching; this is particularly unacceptable for the production of fine chemicals and pharmaceuticals. Heterogeneous asymmetric catalysis provides a good way to resolve such problems and has recently attracted a great deal of interest [27-30].

2.5 Heterogeneous Asymmetric Catalyst

Increasing demand for nonracemic chiral chemicals, the development of efficient methods to provide enantiomerically enriched products is of great current interest to both academia and industry [27-30, 34-36]. Among the various approaches employed for this purpose, asymmetric catalysis constitutes one of the most general and appealing strategies in terms of chiral economy and environmental considerations [4-9]. Over the past few decades, intense research in this field has greatly expanded the scope of catalytic reactions that can be performed with high enantioselectivity and efficiency. Consequently, thousands of chiral ligands and their transition metal complexes have been developed for the homogeneous asymmetric catalysis of various organic transformations. Despite this remarkable success, however, only a few examples of asymmetric catalysis have been developed into industrial processes, and today most chiral chemicals are still produced from natural chiral building blocks or through the resolution of racemic mixtures. The main concern for this situation is the need for reusable chiral catalysts for industrial implementation. Due to the high cost of both the metal and the chiral ligands, systems that allow the straightforward separation of expensive chiral catalysts from reaction mixtures and efficient recycling are highly desirable.

Heterogeneous catalysis takes place between several phases. Generally the catalyst is a solid, and the reactants are gases or liquids. In contrast with homogeneous catalysts where in theory each individual atom can be catalytically active while in heterogeneous catalysts only the surface atoms are active. Heterogeneous catalysts are either automatically removed in the process (e.g., gas-phase reactions in fixed-bed reactors), or they can be separated by simple methods such as filtration or centrifugation [31].

To date there have been numerous approaches to the design of heterogeneous asymmetric catalysts, since Schwab and coworkers first demonstrated that Cu and Ni could be supported on chiral silica surfaces [33] and that the resulting catalysts could give low enantioselection in the dehydration of butan-2-ol. Figure 2.4 shows three models of heterogeneous asymmetric catalysis, i.e. *chirally modified solid surfaces*, *attachment of chiral auxiliaries to reactant* and *intrinsically chiral solid or surface*.

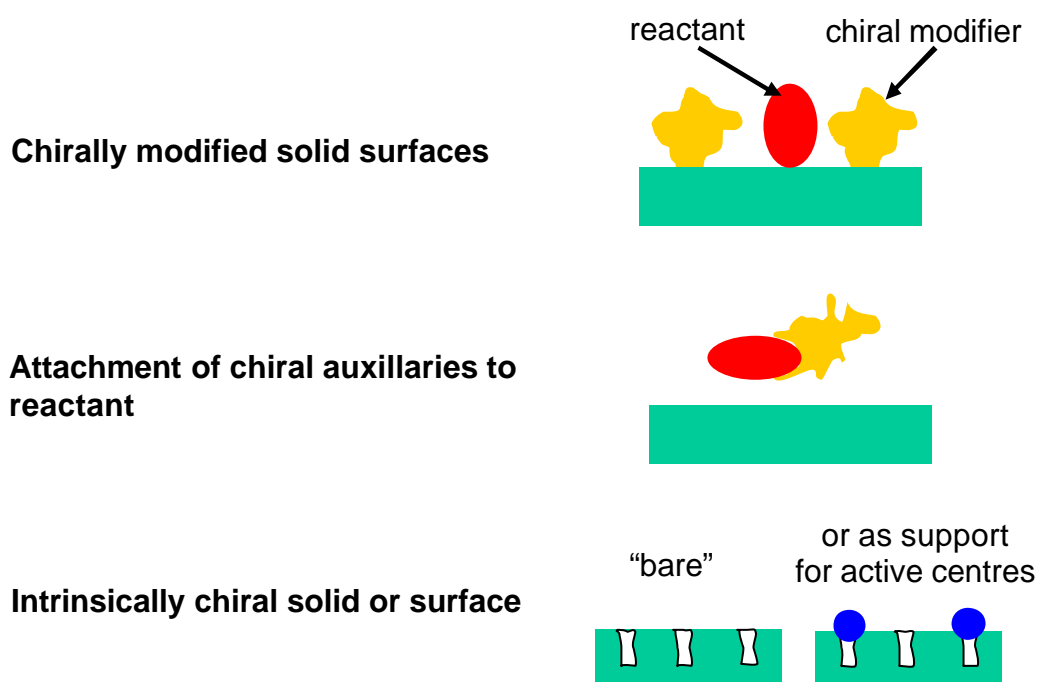


Figure 2.4: Models of heterogeneous asymmetric catalysis.

Many research efforts have been made to develop asymmetric synthesis using heterogeneous catalysts, such as assembling the chiral catalysts in emulsion and phase-separation media, heterogenization of the chiral catalyst by polymerization, immobilization of chiral catalysts onto solid supports, and so on.⁸ The immobilization of chiral catalysts onto solid supports is the most popular method to prepare heterogeneous asymmetric catalysts. Both the surface and porous matrix of a solid support could be used to anchor the asymmetric active center. The metal complexes can be supported on oxide surfaces, such as by chiral self-dimerization, to create asymmetric oxidative coupling catalysis and surface functionalization with achiral reagents to promote asymmetric catalysis [27-36]. Moreover, the inner pore of a solid support immobilized with chiral catalysts provides a novel chiral space for asymmetric catalysis. Four main approaches have been commonly used to immobilize the chiral catalyst: 1) adsorption of chiral modifiers onto an active metal surface; 2) covalent tethering of homogeneous catalysts; 3) electrostatic interaction between a negatively charged framework and a cation; and 4) encapsulation. Organic and inorganic materials, such as metal oxides, clays, zeolites, activated carbon, porous silica, mesoporous silicas, and polymers have been employed as supports for immobilizing the chiral catalyst [27-36]. The inorganic materials usually have advantages over organic polymers in view of chemical, mechanical, and thermal stabilities.

2.5.1 Modification of Metal/Solid Surfaces with Chiral Molecules

Figure 2.5 summarizes the most important approaches to immobilize or heterogenize soluble catalysts that have been described in the literature. The following materials have been used as supports [30]:

- Linear, non-cross-linked polymers and, more recently, also better defined dendrimers are soluble in suitable solvents and give catalysts with high mobility and good mass transport properties. However, separation is not trivial (precipitation or ultrafiltration).
- Swellable, slightly cross-linked polymers such as polystyrene cross-linked with 0.5-3% 1,4-divinylbenzene, can easily be separated by filtration or

sedimentation. To allow good mass transport, these polymers have to be used in solvents in which they swell.

- Highly cross-linked polymers (e.g. macroreticular polystyrenes or polyacrylates) and inorganic supports (metal oxides, e.g. silica gel) hardly swell and can be used in a large variety of different solvents without changes of texture or mass transport properties.
- For immobilization via entrapment or intercalation, materials such as zeolites or clays with well defined pores and cavities have to be used to effect reliable confinement of the metal complex catalysts.

Immobilization method	Covalent bindings	adsorption	Ion pair formation	Entrapment or 'ship in a bottle'
Applicability	broad	Restricted	Restricted	Restricted
Problem	preparation	competition with solvents, substrates	competition with solvents, substrates	size of substrate, diffusion

Figure 2.5: Schematic view and important properties of immobilized complexes [30].

Heterogeneous-enantioselective hydrogenation of prochiral ketones has been extensively studied using cinchona-modified-supported Pt catalysts [37, 38] and tartrate-modified-supported Ni catalysts [39–41]. However, the hydrogenation of pyruvate esters using cinchonidine-modified Pt/SiO₂ and Pt/? -Al₂O₃ represents the most-well-investigated reactions, and these are often studied as a model system. For

this reaction, the enantioselectivity can be high and enantioselective excess (e.e.) in excess of 90% has been reported in many studies [38-41].

2.5.2 Attachment of Chiral Auxiliaries to Reactant

At present this is one of the most popular approaches for the design of highly efficient heterogeneous asymmetric catalysts. The strategy employed tends to depend on the reaction being catalyzed, but overall this method has the potential for designing generic heterogeneous asymmetric catalysts applicable to many reaction types [36].

2.5.3 Intrinsically Chiral Solid/Surface Catalyst

Comparison to the former two methods, there are very few reports on intrinsically chiral solid/surface catalyst. The only reported “intrinsically” heterogeneous catalytic system to synthesize chiral/enantiomer compound is by BEA type zeolite structure synthesized with a chiral template molecule. However, only 5% enantioselectivity could be achieved [42, 43]. Therefore, it is the greatest challenge to synthesize a highly heterogeneous enantioselective catalyst. Heterogeneous enantioselective catalyst or called chiral solid catalyst is receiving major interest due to their advantages, not only ease to recover, recycling and environmental friendly, but also amenable for continuous processing. Based on the above considerations, in this thesis, a strategy to obtain high activity catalyst in enantioselective hydration of epoxyclohexane is proposed.

2.6 Important Criteria for Enantioselective Catalysts

As a consequence of the peculiarities of enantioselective catalysis described above, the following critical factors often determine the viability of an enantioselective process [30]:

Enantioselectivity, expressed as enantiomeric excess (ex., 5%). The enantioselectivity of a catalyst should be in the range of 99% for pharmaceuticals if further enrichment is not possible (this is relatively rare). E.e.'s >80% are acceptable for agrochemicals or if further enrichment is easy, e.g. via recrystallization or via separation of diastereomers later in the synthesis; this is very often the case.

Catalyst productivity, given as turnover number (TON), determines catalyst costs. In our experience, TONS for (homogeneous) enantioselective hydrogenation reactions ought to be >1000 for small-scale, high-value products and >50000 for large-scale or less expensive products. For C-C coupling reactions and probably also for some other reaction types with high added value or for very inexpensive catalysts, lower TONS.

Catalyst activity. For preparative applications, a useful number is the turnover frequency (TOF) at high conversion. Because this value determines the production capacity, TOFs (especially for high pressure reactions) ought to be >500 h⁻¹ for smallscale and >10000 h⁻¹ for large-scale products. For applications in standard equipment, lower TOFs might be acceptable.

Separation should be achieved by a simple operation such as distillation, filtration or phase separation, and at least 95% of the catalyst should be recovered. Methods like ultrafiltration or precipitation (e.g. for separating soluble polymer supports) usually require expensive equipment.

Stability. If the advantage of the heterogeneous catalyst is its recyclability, it has not only to show a stable catalytic performance, but it should also be mechanically stable and the active component must not leach (chemical stability).

Price of catalysts. The catalyst price will only be important at a later stage, when the cost of goods of the desired product is evaluated. For homogeneous catalysts, the chiral ligand often is the most expensive component (typical prices for the most important chiral phosphines are 100-500 \$/g for laboratory quantities and 5000 to >20000 \$/kg on a larger scale). For heterogeneous systems, the dominant cost elements depend on the type of catalyst.

Availability of the catalysts. If an enantioselective catalyst is not available at the right time and in the appropriate quantity, it will not be applied due to the time limitation of process development. At present, only very few homogeneous catalysts and ligands are commercially available in technical quantities, so that their large-scale synthesis must be part of the process development. The situation for heterogeneous catalyst systems is even more difficult, because their preparation and characterization require know-how that is usually not available in a standard development laboratory.

Which of these criteria will be critical for the development of a specific process will depend on the particular catalyst and transformation, the scale of the process, the technical experience and the production facilities of a company as well as the maturity of the catalytic process.

2.7 Amino Acids

More than 700 amino acids have been discovered in Nature and most of them are α -amino acids. Bacteria, fungi and algae and other plants provide nearly all these, which exist either in the free form or bound up into larger molecules (as constituents of peptides and proteins and other types of amide, and of alkylated and esterified structures) [44, 45].

Amino acids are named as such because each amino acid consists of an amine portion and a carboxylic acid part, as seen below (Figure 2.6).

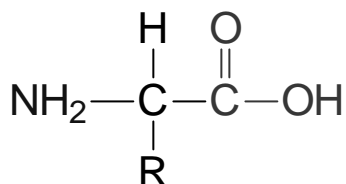


Figure 2.6: An amine portion and a carboxylic acid part in amino acid.

Compare this structure to the above structures of each of the amino acids. Each amino acid has this general structure. The structural formula of some amino acids are shown in Figure 2.7.

The side chains are sometime shown as R-groups when illustrating the backbone. In the approximately 20 amino acids found in our bodies, what varies is the side chain. Some side chains are hydrophilic while others are hydrophobic. Since these side chains stick out from the backbone of the molecule, they help determine the properties of the protein made from them.

The amino acids in our bodies are referred to as alpha amino acids. The reason is that the central carbon is in an alpha position in relation to the carbonyl carbon. The carbon adjacent to the carbonyl carbon is designated the alpha carbon. Each carbon in the chain will be designated with a different letter of the Greek alphabet.

2.7.1 Chirality of Amino Acids

A chiral compound must contain a carbon that is bonded to four different atoms/groups. If you look at the above amino acids you will see that, with the exception of glycine, each structure is chiral around the carbon with the R group. Each amino acid will come in two structural formats, called enantiomers, an L and a D. The location of the hydrogen on the chiral carbon is important to determine which enantiomer. If the hydrogen is on the left, then the amine group is on the right, this is the D enantiomer. If the hydrogen is on the right, then the amine group is on the left, this is the L enantiomer (see Figure 2.8 for structural diagrams).

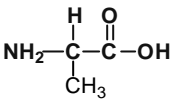
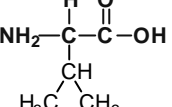
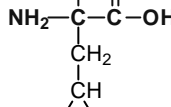
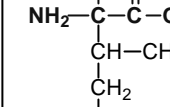
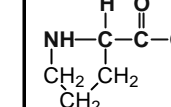
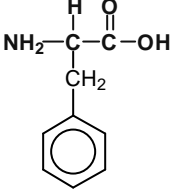
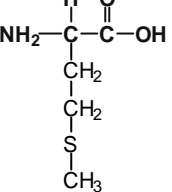
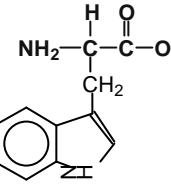
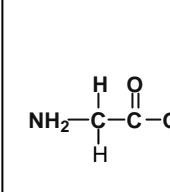
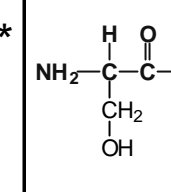
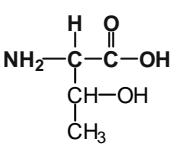
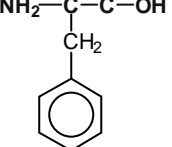
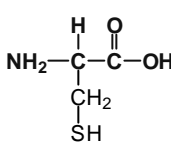
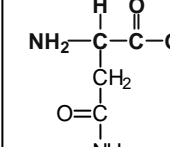
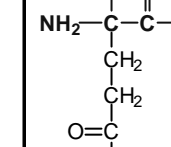
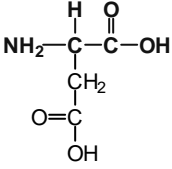
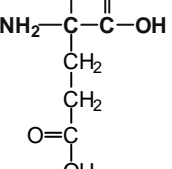
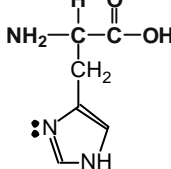
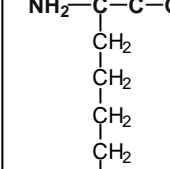
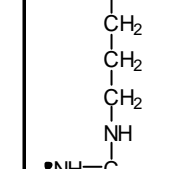
				
alanine ala – A	valine val – V	leucine leu – L	isoleucine ile – I	proline pro – P
				
phenylalanine phe – F	methionine met – M	tryptophan trp – W	glycine* gly – G	serine ser – S
				
threonine thr – T	tyrosine tyr – Y	cysteine cys – C	asparagine asn – N	glutamine gln – Q
				
aspartic acid asp – D	glutamic acid glu – E	histidine his – H	lysine lys – K	arginine arg – R

Figure 2.7: Structural formula of amino acids [46].

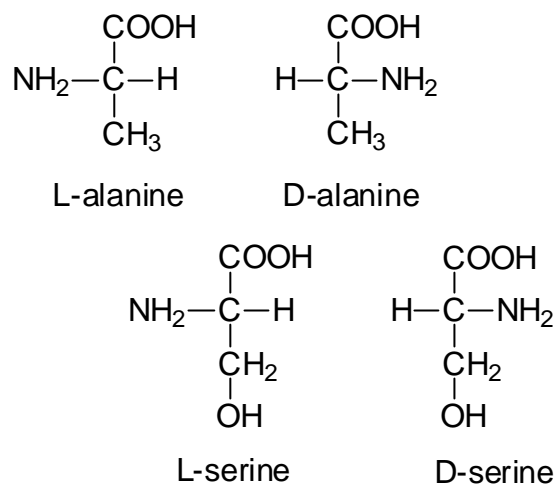


Figure 2.8: Structural diagrams of some amino acids.

The importance of chiral compounds is that their chemical reactivity is different [44, 45]. Sometimes the difference means the compound will have an adverse effect on a person. Sometimes the difference means the person simple cannot metabolize the compound. The latter is the case with amino acids. Meaning we can consume both L and D amino acids, but our bodies will only metabolize the D form. The enzymes used in the metabolism of amino acids are built to fit this D form but not the L form. The L form will pass through your body unused.

2.7.2 The Hydropathy Index of Amino Acids

The hydropathy index of an amino acid is a number representing the hydrophobic or hydrophilic properties of its side-chain. The larger the number is, the more hydrophobic the amino acid. As tabulated in Table 2.1, it is shown that the most hydrophobic amino acids are isoleucine (4.5) and valine (4.2). The most hydrophilic ones are arginine (-4.5) and lysine (-3.9).

Table 2.1: Standard amino acids and their hydropathy indexes [46].

Amino acid	Side chain polarity	Side chain charge (pH 7)	Hydropathy index
Alanine	nonpolar	neutral	1.8
Arginine	polar	positive	-4.5
Asparagine	polar	neutral	-3.5
Aspartic acid	polar	negative	-3.5
Cysteine	nonpolar	neutral	2.5
Glutamic acid	polar	negative	-3.5
Glutamine	polar	neutral	-3.5
Glycine	nonpolar	neutral	-0.4
Histidine	polar	positive	-3.2
Isoleucine	nonpolar	neutral	4.5
Leucine	nonpolar	neutral	3.8
Lysine	polar	positive	-3.9
Methionine	nonpolar	neutral	1.9
Phenylalanine	nonpolar	neutral	2.8
Proline	nonpolar	neutral	-1.6
Serine	polar	neutral	-0.8
Threonine	polar	neutral	-0.7
Tryptophan	nonpolar	neutral	-0.9
Tyrosine	polar	neutral	-1.3
Valine	nonpolar	neutral	4.2

2.8 Octadecyltrichlorosilane

Octadecyltrichlorosilane (OTS, or *n*-octadecyltrichlorosilane) is an organometallic chemical. It is used in semiconductor industry to form self-assembled monolayer thin films on silicon dioxide substrates. Its structural chemical formula is

$\text{CH}_3(\text{CH}_2)_{17}\text{SiCl}_3$. It is flammable, reacts violently with water, and is sensitive to air. It is corrosive and can severely damage mucous membranes. Octadecyltrichlorosilane is an amphiphilic molecule consisting of a long-chain alkyl group ($\text{C}_{18}\text{H}_{37}-$) and a polar head group (SiCl_3-), which forms Self assembled monolayers (SAMs) on various oxidic substrates [47]. Figure 2.9 shows the chemical structure of *n*-octadecyltrichlorosilane (OTS).

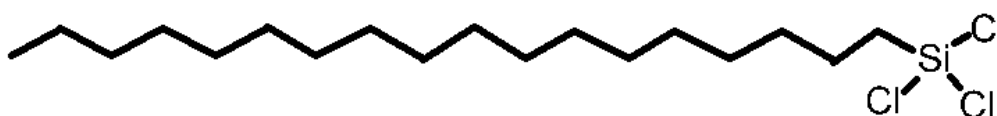


Figure 2.9: Chemical structure of *n*-octadecyltrichlorosilane (OTS).

2.9 Determination of Enantioselectivity by Chiral Column Chromatography

Chiral column chromatography is a variant of column chromatography in which the stationary phase contains a single enantiomer of a chiral compound rather than being achiral [48]. The two enantiomers of the same analyte compound differ in affinity to the single-enantiomer stationary phase and therefore they exit the column at different times.

The chiral stationary phase can be prepared by attaching a suitable chiral compound to the surface of an achiral support such as silica gel, which creates a Chiral Stationary Phase (CSP) [49]. Many common chiral stationary phases are based on oligosaccharides such as cellulose or cyclodextrin (in particular with β -cyclodextrin, a seven sugar ring molecule). As with all chromatographic methods, various different stationary phases are particularly suited to specific types of analytes.

Chiral molecules can elicit very different responses in a biological system, depending on their stereochemistry. Rapid commercial introduction of optically

active drugs requires reliable stereochemical analysis of the products, and of the chiral intermediates used in their synthesis. Capillary gas chromatography is a simple, fast, accurate, sensitive, and reproducible technique for separating stereo and positional isomers of compounds that can be vaporized without decomposition. Chiral separations have been performed by gas chromatography for nearly three decades. First generation chiral GC columns were based on nonbonded and bonded amino acid moieties; the latest capillary GC columns are based on functionalized cyclodextrins.

Cyclodextrins (CDs) are cyclic, chiral, torus-shaped macromolecules composed of 6 or more D(+)-glucose residues bonded through α -(1-4) glycosidic linkage. CDs are classified by the number of glucose residues they contain; α -CDs contain 6 residues (cyclohexaamylose), β -CDs contain 7 (cycloheptaamylose), and γ -CDs contain 8 (cyclooctaamylose) (Figure 2.10). The mouth of the torus-shaped CD molecule has a larger circumference than the base and is linked to secondary hydroxyl groups of the C2 and C3 atoms of each glucose unit (Figure 2.11). The primary hydroxyl groups are located at the base of the torus, on the C6 atoms. Free to rotate, they partially block the base. The size of the cavity increases with increasing number of glucose units, from 4.7-5.2 Å for α -CD to 6.0-6.5 Å for β -CD to 7.5-8.5 Å for γ -CD.

The hydroxyl groups in the glucose units can be selectively functionalized to provide various physical properties and inclusion selectivities. In the last few years enantiomers have been chromatographically separated by using peralkylated α -, β -, and γ -CD dissolved in polysiloxanes and coated within glass or fused silica capillary tubing. Without the cyclodextrin derivative, no enantiomeric selectivity is exhibited. Enantiomers of polar compounds (e.g., alcohols, diols, carboxylic acids) can be separated without previous derivatization on inert fused silica tubing coated with cyclodextrin/polysiloxane phases. Moreover, racemic alkanes and cycloalkanes are separated by such phases. Consequently, cyclodextrin stationary phases have broadened the capabilities of chiral separations into the fields of agriculture, foods, flavors, beverages, environmental samples, petrochemicals, chemicals and natural products.

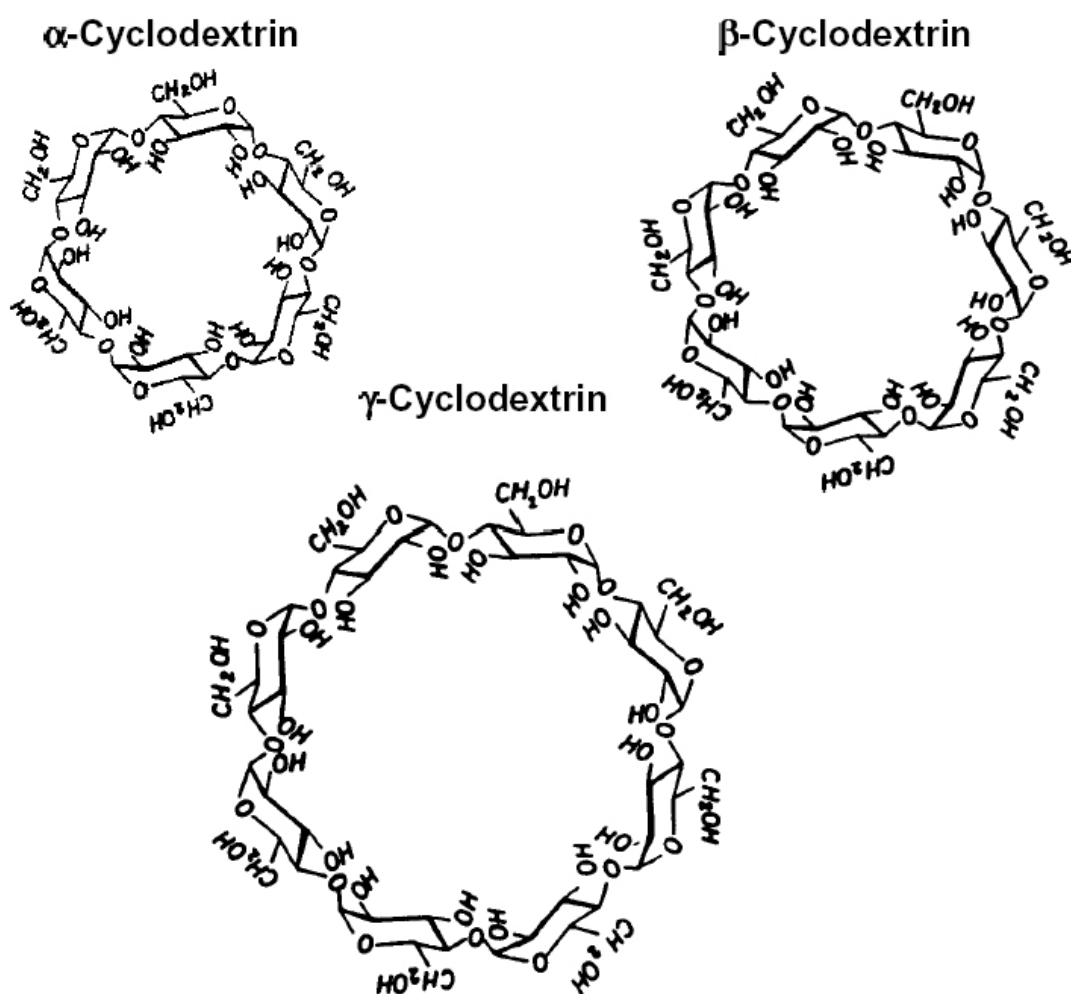


Figure 2.10: Structure of α -, β -, or γ -cyclodextrin (6, 7, or 8 glucose units) [49].

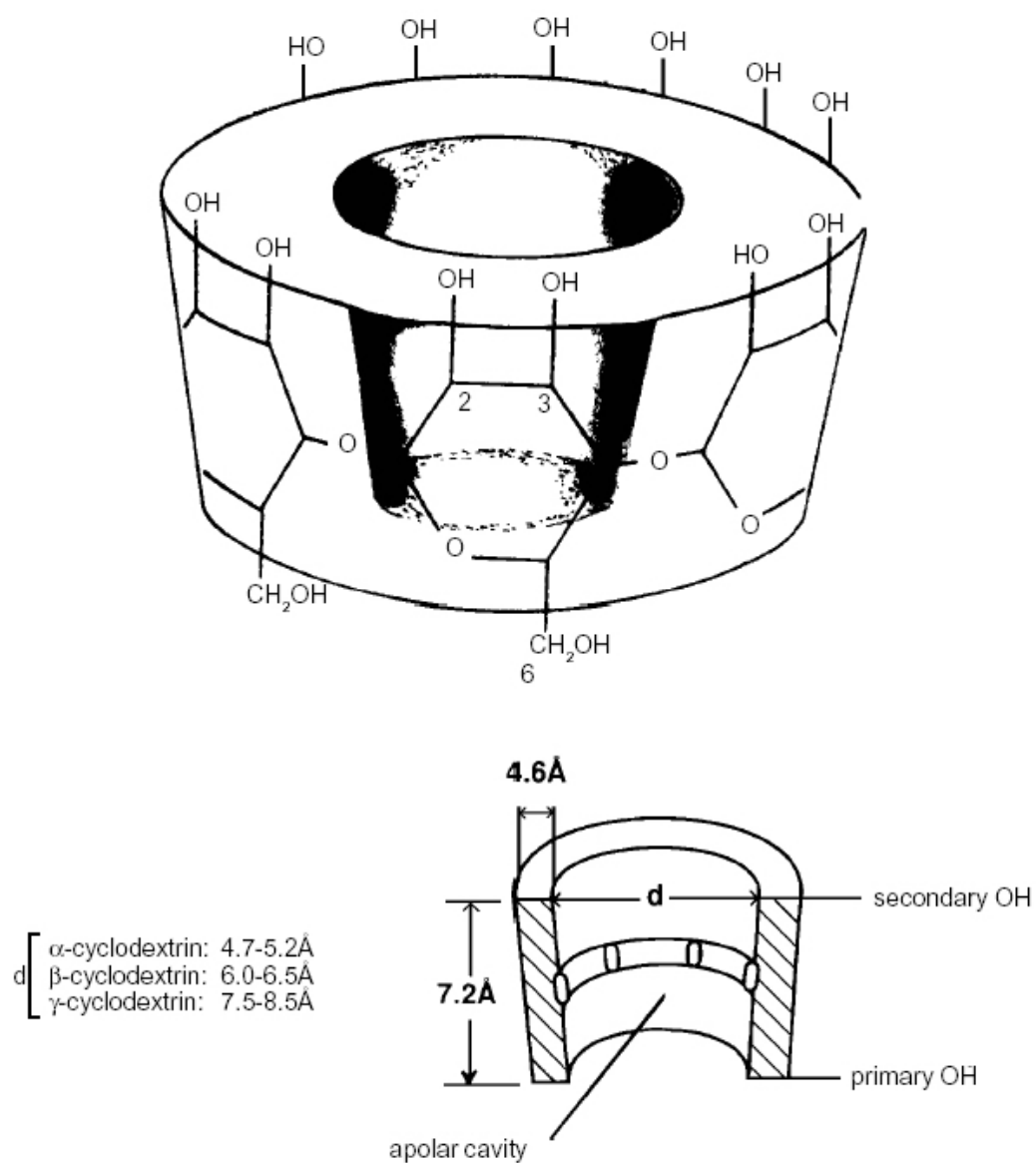


Figure 2.11: Cross section through the cone of α -, β -, or γ -cyclodextrin (6, 7, or 8 glucose units) with the hydroxyl groups outside the cavity and the ring of glycosidic oxygens -O- inside [49].

CHAPTER III

EXPERIMENTAL

3.1 Synthesis of Heterogeneous Asymmetric Catalyst

Three types of heterogeneous asymmetric catalyst were prepared using three types of amino acid as chiral promoter, *i.e.*, L-glutamic acid, L-leucine and L-phenylalanine. The amino acids are attached onto the hydrophilic part of hydrolyzed octadecyltrichlorosilane (OTS) during sol-gel synthesis.

Ten mmol of octadecyltrichlorosilane (MERCK) was added into 20 mmol of L-glutamic acid (BDH). 10 mL of toluene (MERCK) was added into the mixture. The mixture was then stirred at ambient temperature under open atmosphere in order to hydrolyze the OTS. Then resultant solids were washed thoroughly using boiling distilled water to remove free L-Glutamic acid which was not attached to the hydrolyzed OTS and finally dried in oven at 50 °C. The catalyst prepared was denoted as hydrolyzed OTS-Glu. A similar procedure was also carried out to prepare L-leucine (FLUKA) attached to hydrolyzed OTS (denoted as OTS-Leu) and L-phenylalanine (FLUKA) attached to hydrolyzed OTS (denoted as OTS-PheAla).

3.2 Characterizations of Catalyst

The catalysts were characterized by using fourier transform infrared (FTIR), solid-state magic angle spinning nuclear magnetic resonance (MAS NMR), thermogravimetric analysis (TGA) and further study on the dispersibility of catalysts in immiscible organic and aqueous phases.

3.2.1 X-ray Diffraction (XRD) Spectroscopy

X-ray diffraction is a very useful method to define the crystallographic structure whereby no other means is feasible. Every crystalline substance gives a pattern and the same substance always gives the same pattern therefore, X-ray diffraction pattern of a pure substance is like a fingerprint of the substance and in a mixture of substances each produces its pattern independently of the others. The solid matter can generally be described as amorphous and crystalline. In amorphous structure, the atoms are arranged in a random way similar to the disorder we find in a liquid. Meanwhile, in a crystalline structure, the atoms are arranged in a regular pattern, and there is a smallest volume element that by repetition in three dimensions describes the crystal. Thus by using XRD technique the phase presents in the sample and signify whether the solid sample is amorphous or crystalline phase can be identified.

X-ray diffraction (XRD) patterns were collected on a Bruker Advance D8 with Cu K $_{\alpha}$ radiation ($\lambda = 1.5418 \text{ \AA}$) operated at 40 kV and 40 mA. It was used to characterize the crystallinity, structures and phases of the samples. Typically, powder samples were grounded and spread into a sample holder, and finally analyzed. The pattern was scanned in the ranges between 5° to 70° at a step of 0.020° and step time of 1 second.

3.2.2 Dispersibility of Catalysts in Immiscible Organic and Aqueous Phases

In order to establish the hydrophilicity-hydrophobicity property of the catalysts, each hydrolyzed OTS-Glu, hydrolyzed OTS-Leu and hydrolyzed OTS-PheAla sample (0.06 g) was added into an immiscible mixture of 3 mL of toluene and 1 mL of water. Then, the mixture was stirred vigorously at 1000 rpm for 2 h and kept under static condition for 2 h. The capability of the particles to stabilize the liquid-liquid system to form an emulsion was attributed to their hydrophobic-hydrophilic character and hence their surface structure.

The photograph of the emulsion formed in the presence of OTS-amino acid particles was taken under an optical microscope. The methylene blue (dissolved in aqueous phase) was used as an indicator in order to clarify the type of the emulsion, whether oil in water (o/w) or water in oil (w/o).

3.2.3 Solid State Magic Angle Spinning Nuclear Magnetic Resonance

The MAS NMR experiments were performed using Bruker Avance 400 MHz 9.4 T spectrometer. The ^{29}Si MAS NMR spectra were recorded at 79.44 MHz using 4 micro second radio frequency pulses, a recycle delay of 9 seconds and spinning rate of 7.0 kHz using a 4 mm zirconia sample rotor. The ^{13}C NMR, spectra were collected by a Cross Polarization (CP) MAS method at 100.62 MHz with a 3000 μs ^{13}C pulse, 5 second recycle delay and spinning rate of 7.0 kHz using a 4 mm zirconia sample rotor. Both ^{29}Si and ^{13}C NMR chemical shifts were referred to external TMS at 0 ppm.

It is of interest to study the short range order structure of amino acid attached by the hydrolyzed OTS by ^{29}Si as shown in Figure 3.1 and ^{13}C CP/MAS NMR.

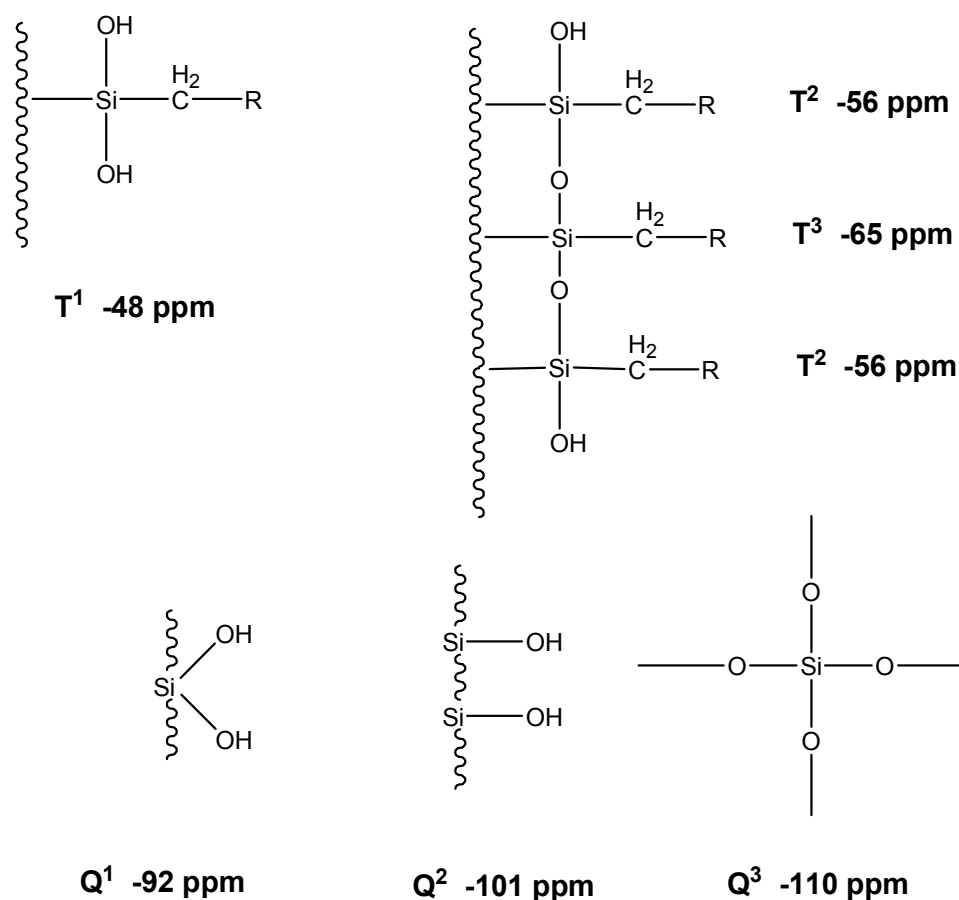


Figure 3.1: Nomenclature and chemical shifts of some silyl species [34, 35].

3.2.4 Fourier Transform Infrared (FTIR)

Fourier transform infrared spectroscopy (FTIR) is used for identifying types of chemical bonds in a molecule by producing an infrared absorption spectrum which by interpreting the infrared absorption spectrum, the chemical bonds in a molecule can be determined. Small differences in structure may result in significant changes in the spectra observed, and absorption in this region is probably unique for every

molecular species. The region is extremely useful for the purpose of identifying a molecule. Molecular bonds vibrate at various frequencies depending on the elements and the type of bonds.

Infrared spectra of the samples were collected on a Perkin Elmer fourier transform infrared (FTIR), with a spectral resolution of 2 cm^{-1} , 10 seconds scan, at temperature of $20\text{ }^{\circ}\text{C}$ by KBr pellet method. The infrared spectra were recorded on Spectrum One FTIR Spectrometer with 4 cm^{-1} resolution. Approximately 1 mg of sample was ground together with 100 mg of potassium bromide using pestle and mortar. The fine powder was then transferred to the 'dye' and 10 ton of pressure was applied for 2 minutes. The resulting pellet was put in the sample holder and the FTIR spectrum of the sample was recorded in the range of 400 cm^{-1} to 4000 cm^{-1} .

3.2.5 Specific Surface Area Analysis

Nitrogen adsorption isotherm is a unique and useful technique in measuring surface area and pore structure of a solid catalyst. The principal method of measuring total surface area of porous structures is by physically adsorption of a particular molecular species in gas form (typically nitrogen) onto the surface of the solid which are maintained at a constant temperature (usually at liquid nitrogen temperature 77K). One of the most commonly used measurements in molecular sieves research is the specific surface area as measured by BET (Brunauer Emmet Teller) method. This method involves adsorbing a monolayer of liquid nitrogen onto a surface of sample followed by measuring the amount of nitrogen that is released when the monolayer is vaporized. Based on this quantity, the surface area of the sample can be calculated.

In this work, the isothermal N_2 adsorption/desorption experiments were conducted on a Quantachrome Autosorb 1 Nitrogen adsorption system. Prior to analysis, samples were outgassed at $100\text{ }^{\circ}\text{C}$ under vacuum for 20 h. The relative pressure P/P_0 (P and P_0 are the pressures of N_2 vapor at adsorption and its saturation vapor pressure at 77 K , respectively) used for the calculation is in the range of 0–0.3.

3.2.6 Thermogravimetric Analysis (TGA)

Study on the adsorption capacity of adsorbed water was carried out in order to determine hydrophilicity relative of the samples. The samples were dehydrated under vacuum at 100 °C overnight. After dehydration, the sample was exposed to water vapor at room temperature in the desiccators, followed by the determination of the percentage of adsorbed water using TGA analysis.

Thermogravimetric analyses were performed using a Mettler Toledo TGA-SDTA 851^e. TGA thermal curve was recorded using 70 μ L platinum sample pan filled with approximately 20 mg of sample. TGA analyses performed in air atmosphere with and increment of 5 °C per min from 25 °C to 125 °C and follow by increment of 10 °C per minute to 1000 °C.

3.3 Catalytic Performances

Performances of synthesized heterogeneous asymmetric catalysts are tested using hydration of epoxycyclohexene as model reaction. The hydration of epoxycyclohexene to cyclohexanediol, in principle, yields 3 norbornene adducts: two diastereoisomers, namely *trans*-1,2-cyclohexanediol and *cis*-1,2-cyclohexanediol and two enantiomers, *R* and *S* for *trans*-1,2-cyclohexanediol Figure 3.2.

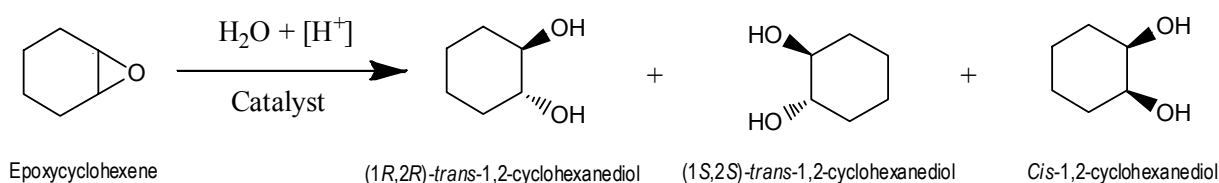


Figure 3.2: Hydration of epoxycyclohexane to 1,2-cyclohexanediol.

The hydration of epoxycyclohexene to 1,2-cyclohexanediol was performed as follows. The catalyst particles (50 mg) were placed in a glass tube and then 10 μ mol of 0.1 M H₂SO₄ was added to the catalysts. Then 50 mmol of epoxycyclohexane

(Merck, > 99%) was added to the solid catalyst wetted with H₂SO₄ and reacted for 20 hours at room temperature under stirring condition. The products of the reaction were analyzed by Agilent Model 7890N Gas Chromatography (GC) using ChiralDEX B-DM capillary column containing 2,3-di-*O*-methyl-6-*t*-butyl silyl derivative of β -cyclodextrin with length and internal diameter 40 m x 0.25 mm. 1 μ L of the sample was injected into the GC inlet with the split ratio 100:1. The oven condition as follows, initial temperature 50 °C, ramp at 4.3 °C per minute to reach 120 °C, hold for 9 minutes, and finally ramp at increment of 5 °C per minute to reach 160 °C with a constant flow of 1.7 mL per minute.

Commercial samples, *i.e.*, *Cis*-1,2-cyclohexanediol (Aldrich, > 99%), (1*S*,2*S*)-*trans*-1,2-cyclohexanediol (Fluka, > 99%) and (1*R*,2*R*)-*trans*-1,2-cyclohexanediol (Fluka, > 99%) were used to determine the products. The enantiopurity or enantiomeric excess (e.e.) of the 1,2-cyclohexanediol is determined by the following equation,

$$\% (e.e.) = \{([R] - [S]) / ([R] + [S])\} \times 100$$

in which % e.e. is percentage of enantiomeric excess, [R] is mmol of R product and [S] is mmol of S product.

CHAPTER IV

RESULTS AND DISCUSSION

4.1 Physical Properties

Figure 4.1 shows the XRD patterns of OTS-Glu, OTS-Leu and OTS-PheAla. In Fig. 4.1, the results of XRD patterns revealed that the all three OTS-amino acids samples are amorphous.

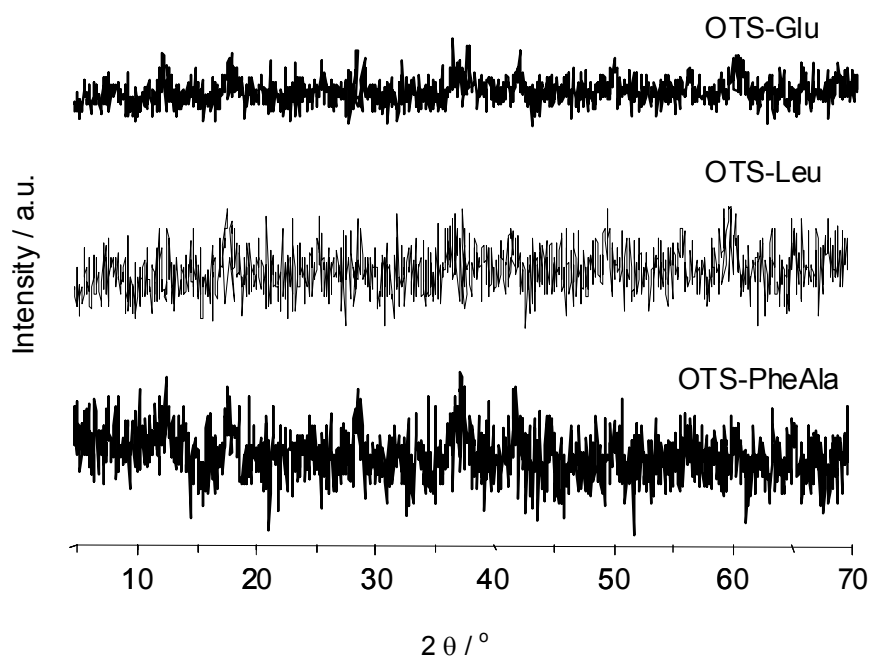


Figure 4.1: XRD patterns of OTS-Glu, OTS-Leu and OTS-PheAla.

In heterogeneous catalysis, the surface area of solid catalyst is the other physical properties which need to be considered. Table 4.2 shows the BET surface area of OTS-Glu, OTS-Leu and OTS-PheAla. From the nitrogen adsorption analysis and XRD results, we could therefore conclude that all three OTS-amino acids are amorphous materials with relatively low surface area.

Table 4.1: BET surface area of OTS-Glu, OTS-Leu and OTS-PheAla.

Catalysts	BET Surface Area m ² / g
OTS-Glu	23
OTS-Leu	19
OTS-PheAla	21

4.2 Hydrophilicity-Hydrophobicity of Catalysts

As shown in Figure 4.2, when the hydrolyzed OTS-Glu particles were added to a mixture of 3 mL toluene and 1 mL water, they were feasibly located at the organic phase. In order to rationalize the hydrophilicity-hydrophobicity of catalysts one should consider the formation of emulsion, because in this form the specific interfacial interactions between the solid catalyst surface and the two immiscible liquid phases increase the surface contact (wettability) of the catalyst with the reactants. For maximum efficiency, the catalyst should be wetted preferentially by the two liquid phases. If the solid particles are too strongly wetted by either of the two liquid phases the required stabilizing action will not occur. Based on these considerations, the formation of the emulsion in the presence of the solid particles was examined. It was observed that an emulsion was formed in the system containing hydrolyzed OTS-Glu particles under stirring condition. As shown in Figure 4.2, it is clearly demonstrated that an emulsion has been formed, resulting in

an abrupt visual homogenization. This suggests that the flexibility of the hydrophobic octadecyl groups allows the formation of micellar aggregates in the system containing immiscible organic and aqueous phases. When the stirring process is stopped after 2 h, the OTS-amino acid particles are observed to settle back slowly (*ca.* 5 min) into organic phase (see Figure 4.2).

The photograph of the emulsion formed in the presence of OTS-Glu particles was taken under an optical microscope. The methylene blue (dissolved in aqueous phase) was used as an indicator in order to clarify the type of the emulsion, whether oil in water (o/w) or water in oil (w/o). Figure 4.3 shows the optical microscope photograph of the type of emulsion formed; the OTS-Glu act as emulsifiers to stabilize the toluene and water mixture forming the water-in-oil type emulsion.

4. 3. Solid State Nuclear Magnetic Resonance

The structural information about the chemically modified material can be obtained by means of Solid-State NMR spectroscopy. In solid state samples, due to the limited motion, strong dipolar-dipolar and chemical shift anisotropy interactions occur. The line broadening effects can be cancelled using magic angle spinning (MAS) technique.

Figures 4.4 show the ^{13}C CP/MAS NMR spectra of hydrolyzed OTS, L-glutamic acid and hydrolyzed OTS-Glu. The NMR spectrum of hydrolyzed OTS-Glu shows the major signals at 177.0 and 1774.1 ppm which provides strong evidence for the prevalence of $-\text{COOH}$ group of L-glutamic acid while major signals at 47.2 ppm indicates the C2 of the amino groups in the L-glutamic acid. The strong signal at 29.1 ppm corresponds to C3 of alkylsilyl group of hydrolyzed OTS. It is clearly observed that the peak of C1 and C5 of $-\text{COOH}$ groups of L-glutamic acid attached to hydrolyzed OTS were shifted towards a higher magnetic field in comparison to that of pure L-glutamic acid (Figure 4.4).

It is clearly observed that after hydrolyzed with OTS, C2 of the amino groups was also shifted to higher magnetic field in the hydrolyzed OTS-Glu. The shifting of

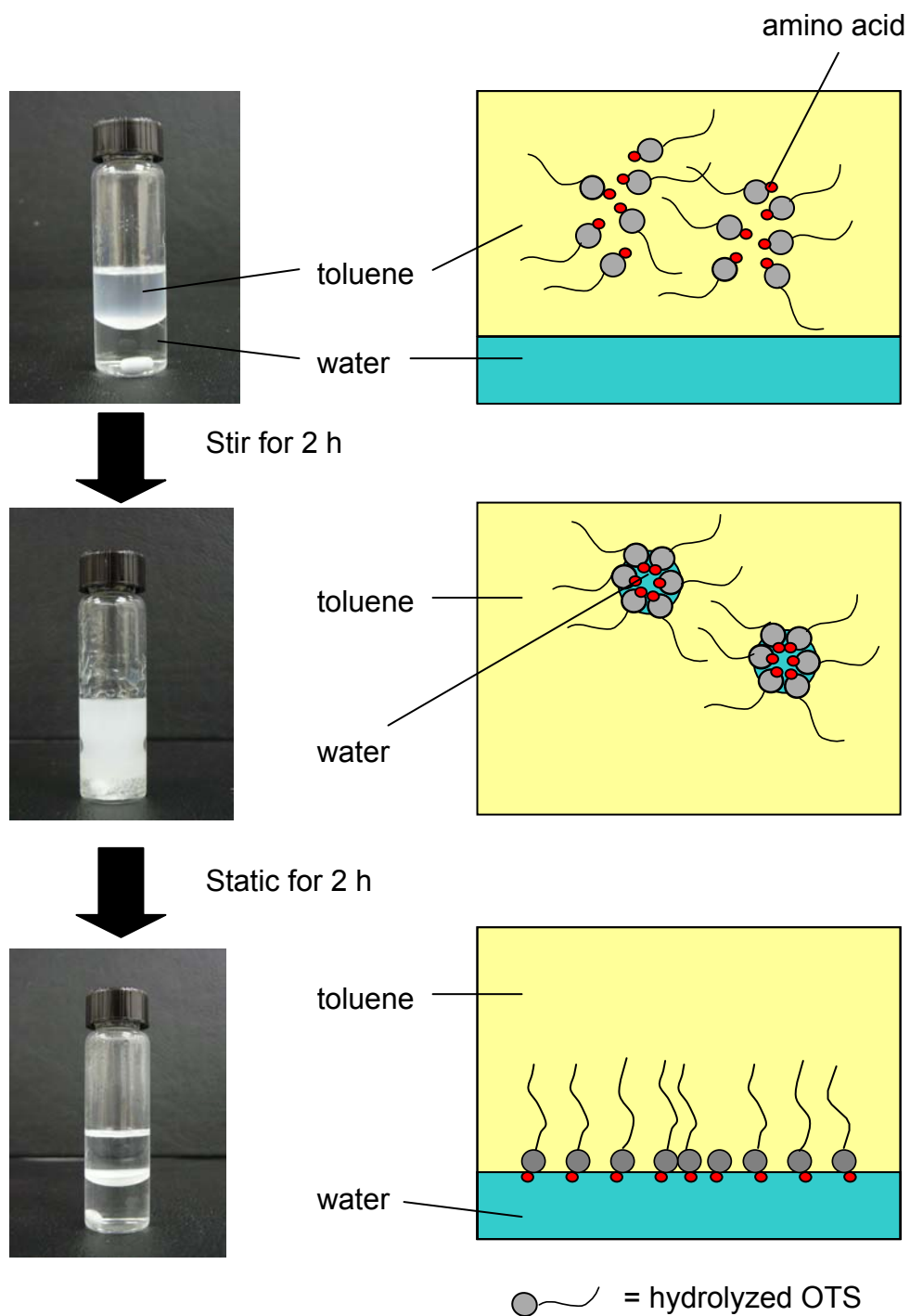


Figure 4.2: Dispersibility of hydrolyzed OTS-Glu in a mixture of toluene and water under stirring and static conditions.

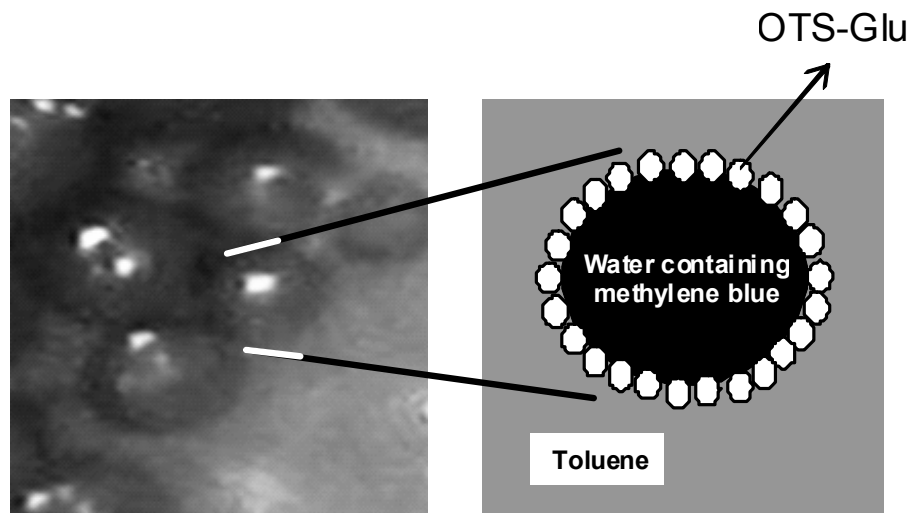


Figure 4.3: Photograph of w/o type of emulsion stabilized by OTS-Glu. Photograph was taken from the emulsion after 2 h under stirring condition.

the peaks of ^{13}C of $-\text{COOH}$ and C3 in alkylsilyl group was also observed for hydrolyzed OTS-Leu (Figure 4.5). In the case of hydrolyzed OTS-PheAla (Figure 4.6), it was observed that the C2 peaks of $-\text{COOH}$ shifting towards a lower magnetic field. The shifting of the ^{13}C CP/MAS NMR signals can be explained by the interaction of the free electron pairs of the oxygen atoms of carboxyl functional group of the amino acids with hydrolyzed OTS. A summary of the NMR result obtained is presented in Table 4.2.

Figure 4.7 shows the ^{29}Si MAS NMR of hydrolyzed OTS and hydrolyzed OTS-Leu. The intense peak at chemical shift (δ) of -110 ppm is from $\text{Si}(\text{3SiO})$ in the hydrolyzed OTS. In Figure 4.6, it is observed that three additional peaks from chemical shift (δ) of -50 ppm to chemical shift (δ) of -80 ppm correspond to three different environments of the siloxane groups in the hydrolyzed OTS-Leu [50, 51]: (i) isolated groups that are not bound to any neighbouring siloxanes (ii) terminal groups that are only bound to one neighbouring siloxane, and (iii) cross-linked groups that are bound to two neighbouring siloxane. However the peak at chemical shift (δ) of -110 ppm from $\text{Si}(\text{3SiO})$ is not observed in the case of hydrolyzed OTS-Leu. Based on the above results, it is suggested that the present of amino acid during

sol-gel synthesis of the hydrolyzed OTS-Leu inhibits the formation of Si(3SiO) bonding in the sample. This result suggested that the amino acid was attached by cross-linked $-(OH)Si(R)-O-(OH)Si(R)-$ of hydrolyzed OTS.

Table 4.2: ^{13}C chemical shift in OTS-Glu, OTS-Leu and OTS-PheAla in comparison to hydrolyzed OTS and pure amino acids.

Samples	Chemical shift (δ) / ppm	
	C in $-COOH$ of amino acid	C in $-C-NH_2$
OTS-Glu	177.0 and 174.1	51.7
L-glutamic acid	172.7 and 170.7	47.2
OTS-Leu	173.3	52.4
L-leucine	174.6	51.7
OTS-PheAla	172.4	55.1
L-phenylalanine	181.8	65.1

4.4 Fourier Transform Infrared

Figure 4.8 demonstrates the FTIR spectra of L-glutamic acid and hydrolyzed OTS-Glu. The spectra are consistent with the skeletal vibration observed in L-glutamic acid. The peak at around 1641 cm^{-1} and 1420 cm^{-1} is corresponded to the asymmetric and symmetric stretch of $COOH$, respectively. Besides that, the strong bend at 1660 cm^{-1} and 1511 cm^{-1} are attributed to the asymmetric and symmetric stretching of NH groups. The broad stretch occurs around 3080 cm^{-1} also indicates the presence of NH ion. The interaction of hydrolyzed OTS with L-glutamic acid can be observed by the shifted of $N-H$ asymmetric stretch to higher field (from 1660 to 1727 cm^{-1}) while the weakening of $N-H$ symmetric at 1511 cm^{-1} was observed. The observation for the asymmetric and symmetric stretching of $COOH$ groups found

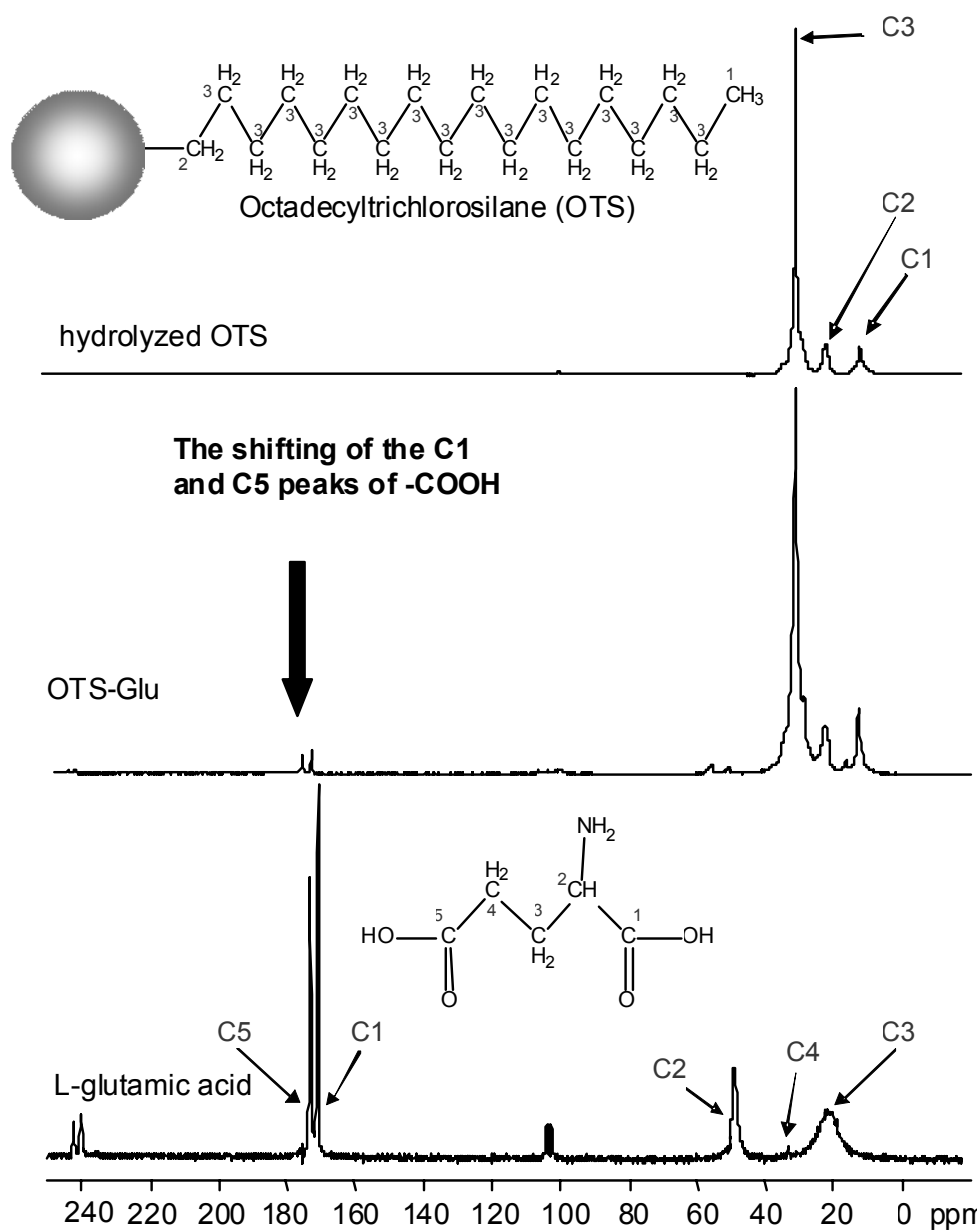


Figure 4.4: ^{13}C CP/MAS NMR of hydrolyzed OTS, L-glutamic acid (Glu) and OTS-Glu.

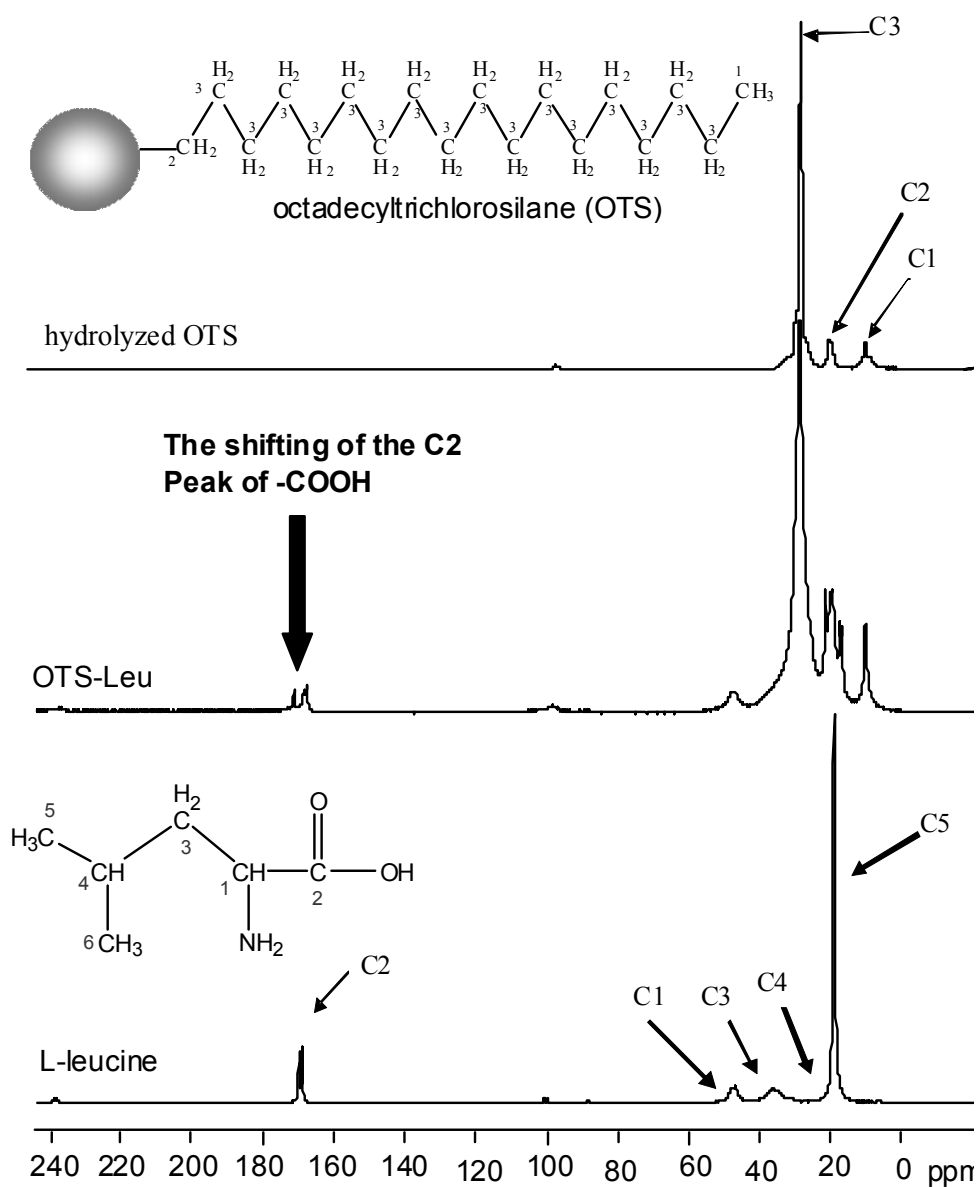


Figure 4.5: ^{13}C CP/MAS NMR of hydrolyzed OTS, L-leucine (Leu) and OTS-Leu.

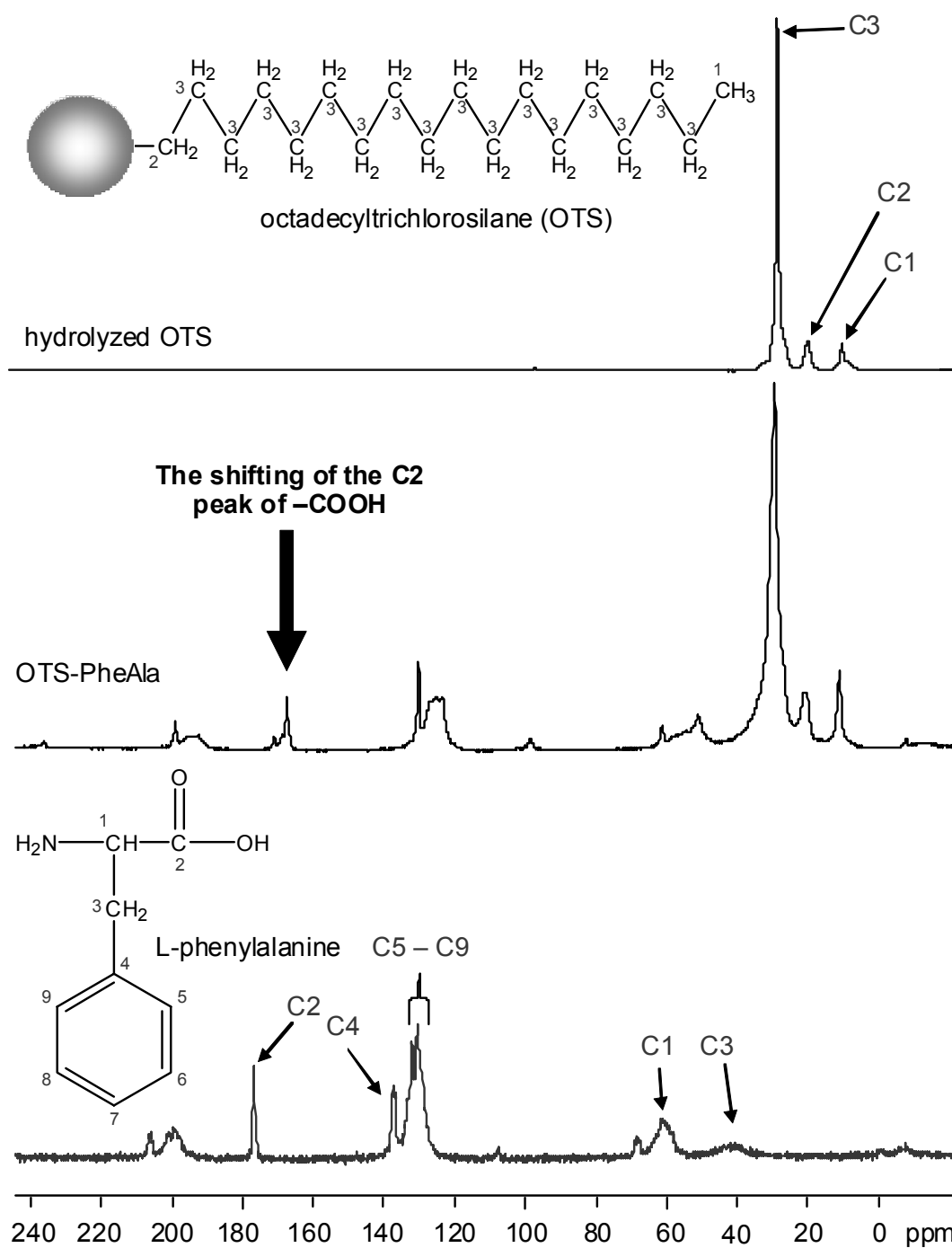


Figure 4.6: ^{13}C CP/MAS NMR of hydrolyzed OTS, L-phenylalanine (PheAla) and OTS-PheAla.

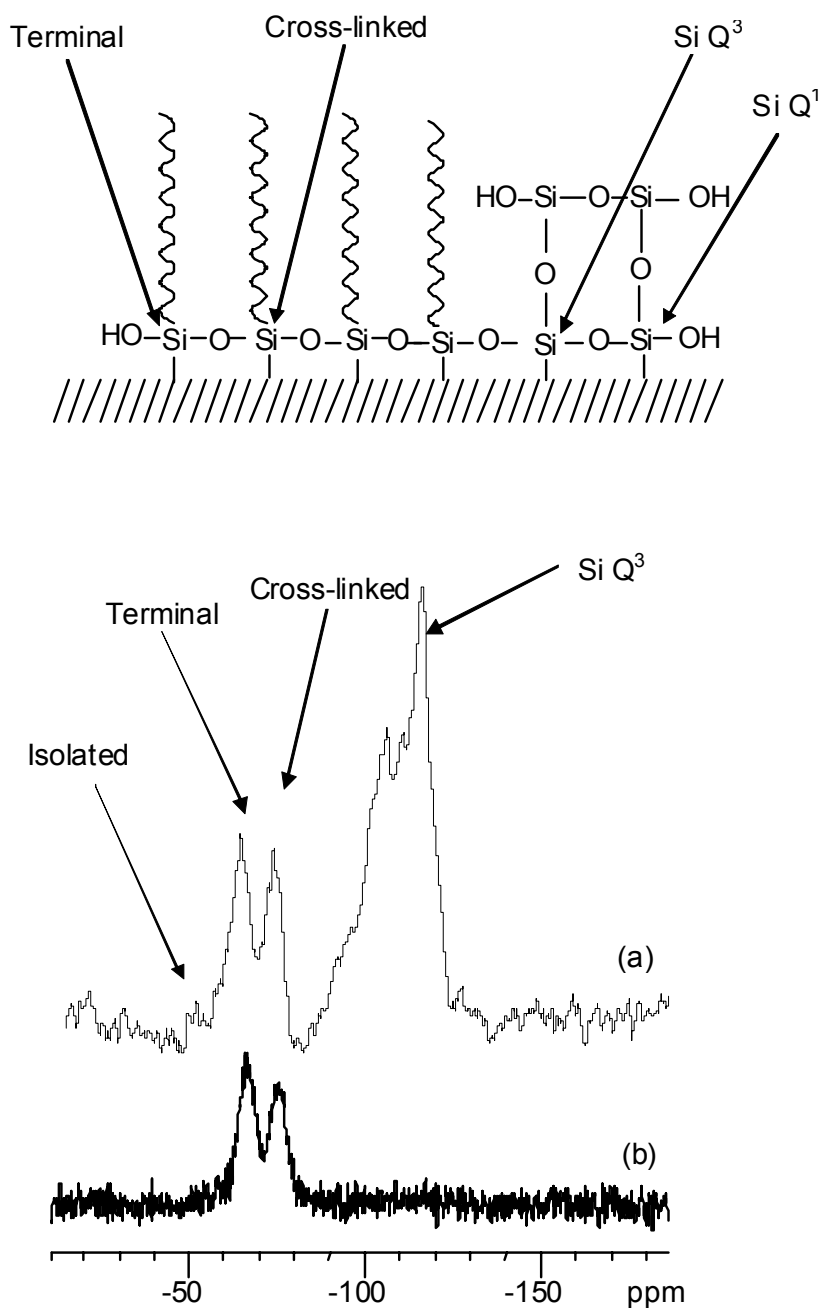


Figure 4.7: ^{29}Si NMR of (a) hydrolyzed OTS and (b) OTS-Leu.

that the strong asymmetric stretch of COOH groups at 1641 cm^{-1} and symmetric from the hydrolyzed OTS. The presents of sp^3 C-H stretch around 3000 cm^{-1} , CH_2 and CH_3 groups at 1469 cm^{-1} and 1353 cm^{-1} and CH_2 long chain band stretch at 719 cm^{-1} stretch of COOH groups at 1420 cm^{-1} were weaken. The absorption band at around 1125 cm^{-1} and 1031 cm^{-1} are assigned to the bending vibration of Si-O-Si

groups confirms the presents of long alkyl chains from the OTS. Figure 4.9 demonstrates the FTIR spectra of L-leucine and hydrolyzed OTS-Leu. The spectra are consistent with the skeletal vibration observed in L-leucine. The peak at around 1581 cm^{-1} and 1407 cm^{-1} is corresponded to the asymmetric and symmetric stretch of COOH. The strong bend 1609 cm^{-1} and 1513 cm^{-1} are attributed to the asymmetric and symmetric stretching of NH groups. The broad stretch occurs around 3080 cm^{-1} also indicates the presence of NH ion.

The interaction of hydrolyzed OTS with L-leucine can be observed by the shifted of N-H asymmetric stretch to higher field (from 1609 to 1692 cm^{-1}) and the weakening of N-H symmetric at 1510 cm^{-1} . The observation for the asymmetric and symmetric stretch of COOH groups suggested that the strong asymmetric stretch of COOH groups at 1581 cm^{-1} were weaken whereas the symmetric stretch of COOH groups disappeared. The absorption band at around 1139 and 1024 cm^{-1} are assigned to the bending vibration of Si-O-Si groups from the hydrolyzed OTS. The presents of sp^3 C-H stretch around 2920 cm^{-1} , CH_2 and CH_3 groups at 1469 cm^{-1} and 1369 cm^{-1} and CH_2 long chain band stretch at 720 cm^{-1} confirms the presents of long alkyl chains from the OTS.

Figure 4.10 demonstrates the FTIR spectra of L-phenylalanine and hydrolyzed OTS-PheAla. The spectra are consistent with the skeletal vibration observed in phenylalanine. The peak at around 1562 cm^{-1} and 1409 cm^{-1} is corresponded to the asymmetric and symmetric stretch of COOH. The strong bend 1640 cm^{-1} and 1562 cm^{-1} are attributed to the asymmetric and symmetric stretching of NH groups. The broad stretch occurs around 3000 cm^{-1} also indicates the presence of NH ion. The interaction of hydrolyzed OTS with L-phenylalanine can be observed by the shifted of N-H asymmetric stretch to higher field (from 1609 to 1735 cm^{-1}) while the increment signal of N-H symmetric at 1484 cm^{-1} was observed. The observation for the asymmetric and symmetric stretch of COOH groups found out that the strong asymmetric stretch of COOH groups at 1562 cm^{-1} were weaken whereas the symmetric stretch of COOH groups disappeared. The absorption band at around 1133 and 1049 cm^{-1} are assigned to the bending vibration of Si-O-Si groups from the hydrolyzed OTS. The presents of sp^3 C-H stretch around 2919 cm^{-1} , CH_2

and CH_3 groups at 1424 cm^{-1} and 1359 cm^{-1} and CH_2 long chain band stretch at 700 cm^{-1} confirms the presence of long alkyl chains from the OTS.

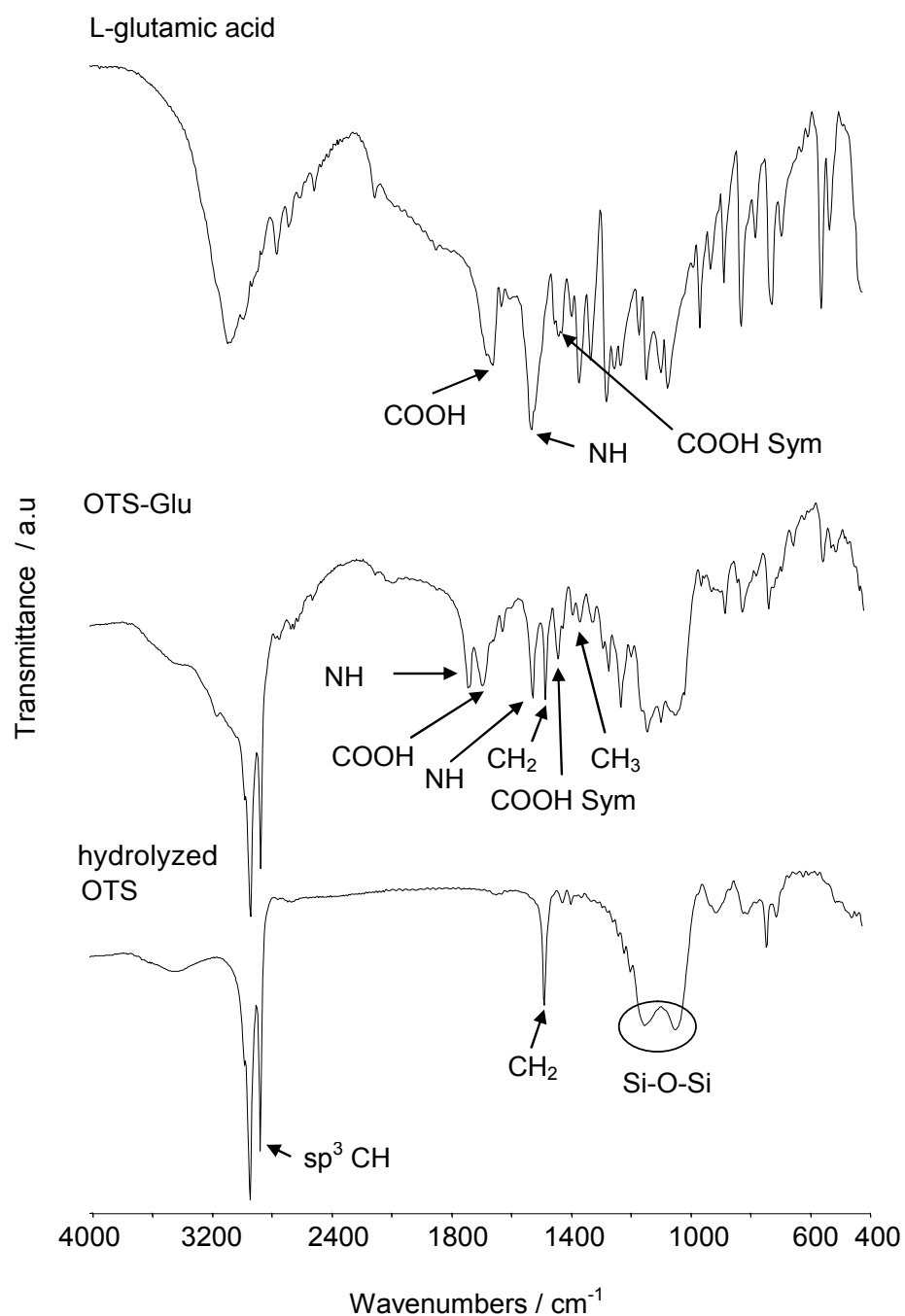


Figure 4.8: FTIR spectra of L-glutamic acid, OTS-Glu and hydrolyzed OTS.

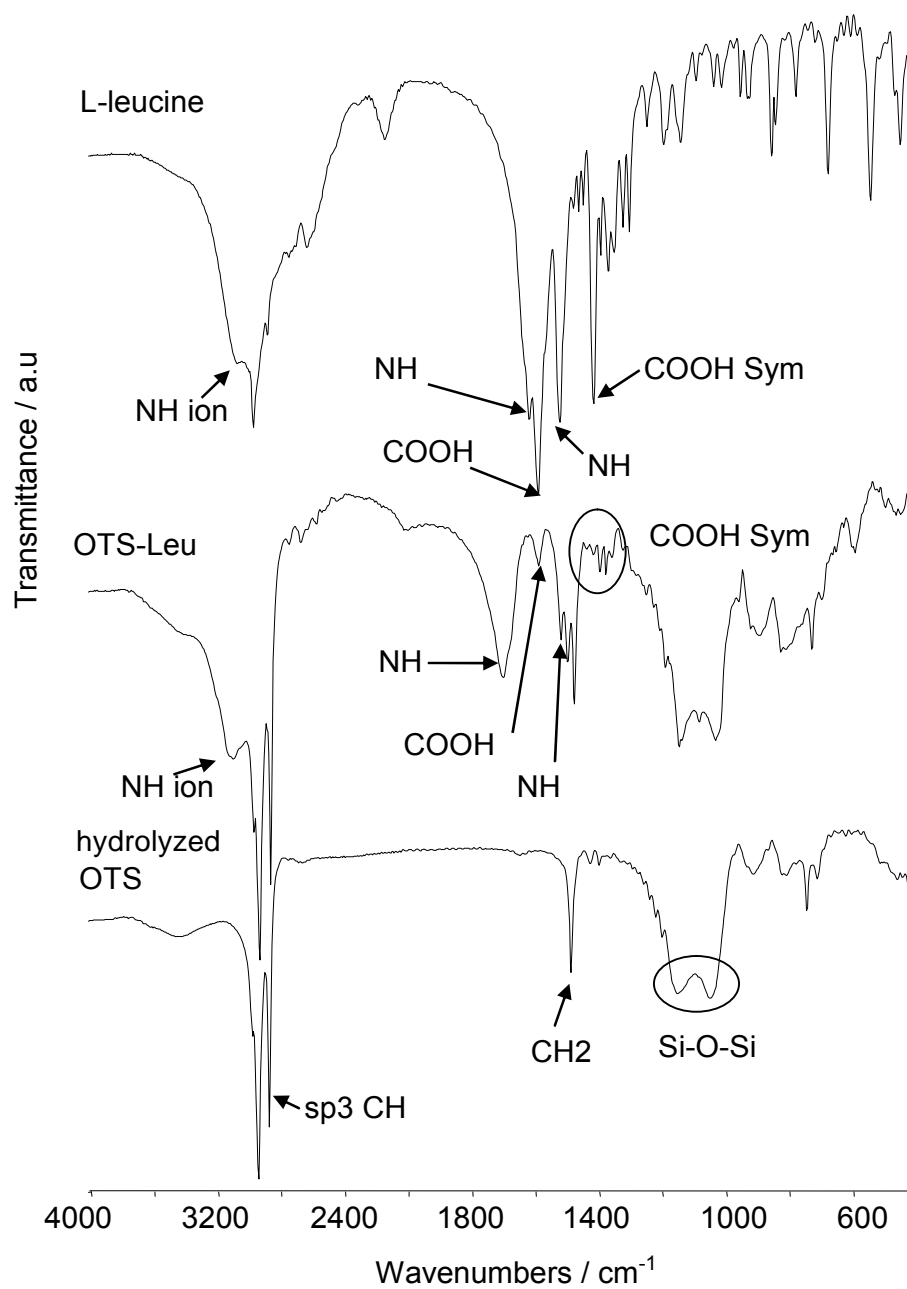


Figure 4.9: FTIR spectra of L-leucine, OTS-Leu and hydrolyzed OTS.

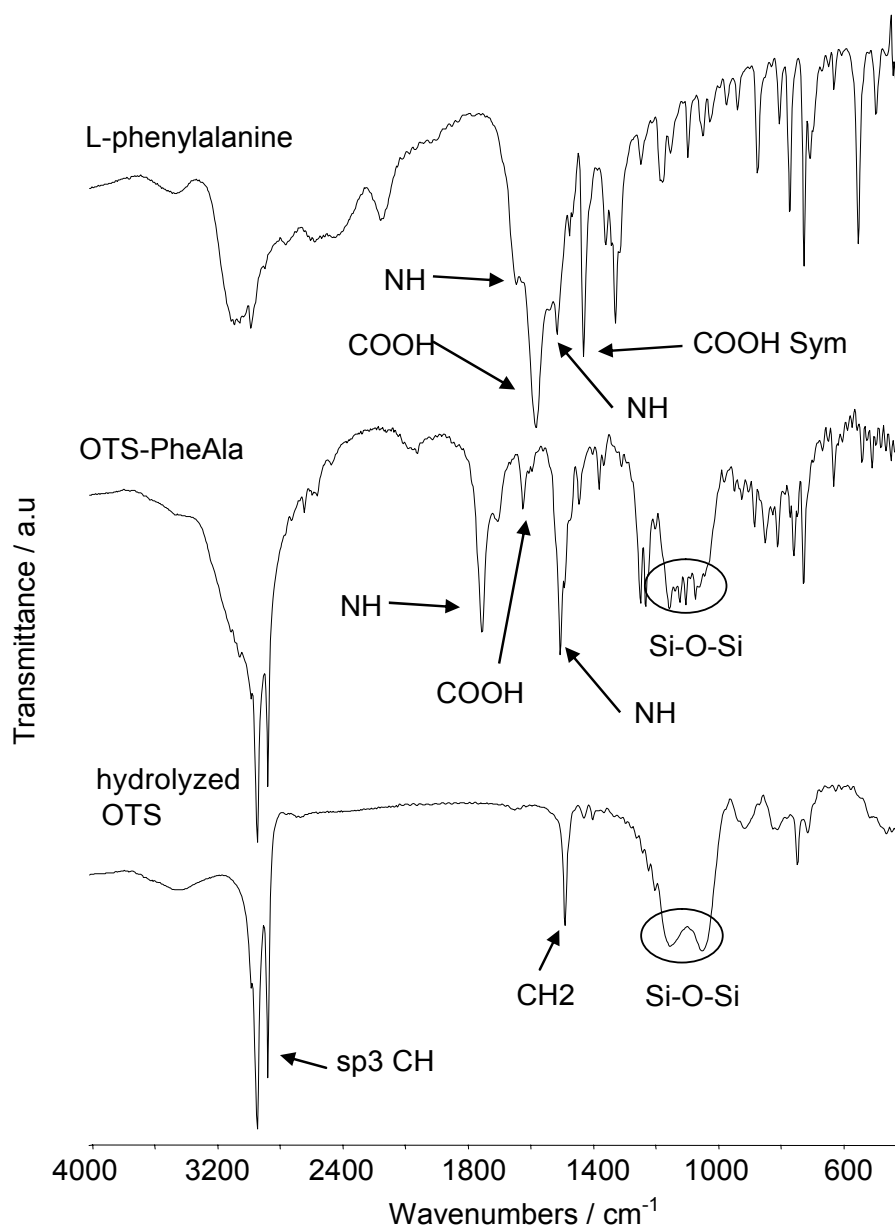


Figure 4.10: FTIR spectra of L-phenylalanine, OTS-PheAla and hydrolyzed OTS.

4.5 Thermogravimetric Analysis

Figure 4.11 shows the thermograms results of adsorption capacity of water in OTS-amino acids. From the thermal analysis, OTS-Glu adsorbs 52% of water vapour, OTS-PheAla 49% and OTS-Leu 19.5%. This indicates that OTS-Glu is more hydrophilic than OTS-PheAla followed by OTS-Leu. This can be explained using the hydrophathy index. The hydrophathy index of an amino acid is a number representing the hydrophobic or hydrophilic properties of its side-chain. The higher of the hydrophathy index number is, the more hydrophobic the amino acid. The results of this study are consistent with hydrophathy index of the amino acid proposed by Jack Kyte and Russell Doolittle [52] where L-glutamic acid has a number of -3.5, L-phenylalanine 2.8 and L-leucine 3.8 which L-glutamic acid with higher hydrophathy index number is more hydrophilic than L-phenylalanine and L-leucine. Figure 4.12 shows the relationship of hydrophathy index with the hydrophobicity of the OTS-amino acids studied. TGA studied on water absorption of OTS-amino acids shows consistent increase in water adsorption capability when hydrophilicity increases (hydrophathy index decreases).

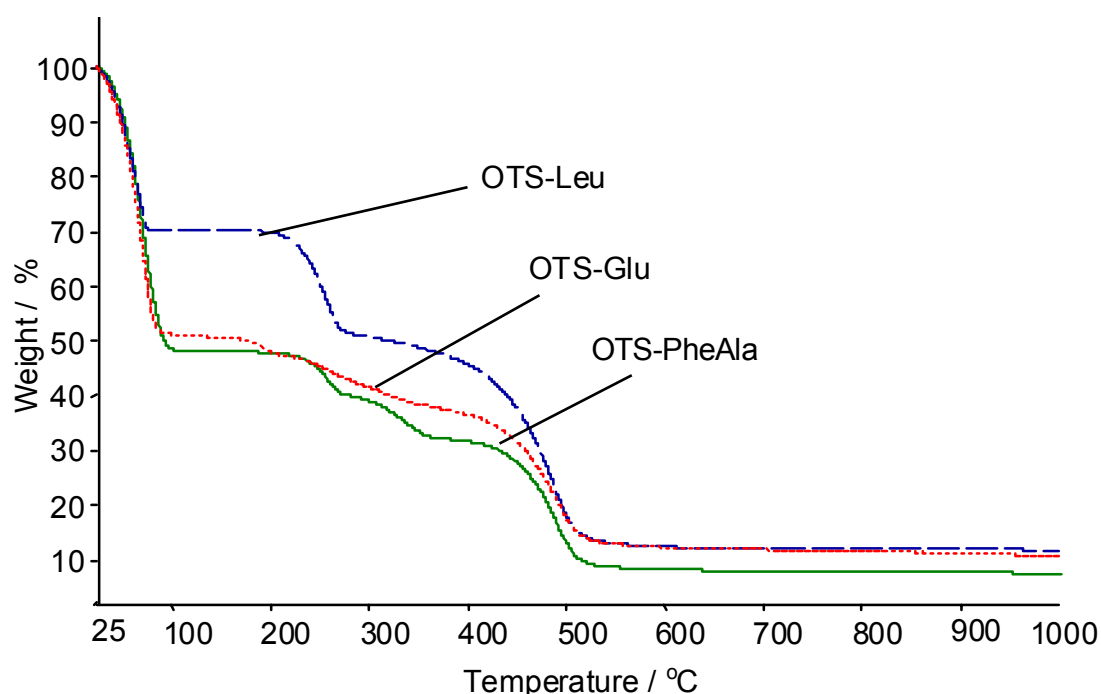


Figure 4.11: Thermograms (TGA) of water absorption on OTS-amino acids.

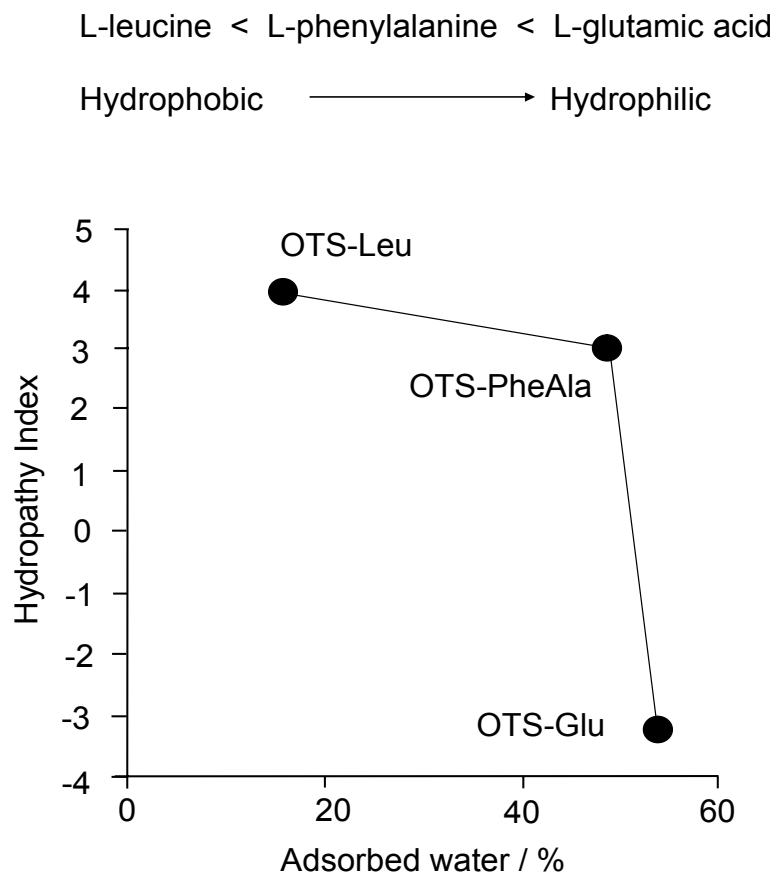


Figure 4.12: Relationship between hydropathy index and percentage of adsorbed water of OTS-amino acids.

4.6 Enantioselective Hydration of Epoxycyclohexane

The main products of the hydration of epoxycyclohexane with sulfuric acid using acetone as solvent over OTS-amino acids were *cis*-1,2-cyclohexanediol, (1*S*,2*S*)-*trans*-1,2-cyclohexanediol and (1*R*,2*R*)-*trans*-1,2-cyclohexanediol. The yield of products was tabulated by Table 4.3. From the results, it is observed that the yields from the OTS-amino acids were enhanced by *ca.* 10 times from those of pure amino acids.

Table 4.3: Reaction yields of hydration of epoxycyclohexane.

Catalyst	Yield / μmol	<i>trans</i> -1,2- cyclohexanediol / μmol	<i>cis</i> -1,2- cyclohexanediol / μmol
OTS-PheAla	17.4	14.9	2.5
OTS-Leu	10.6	8.7	1.9
OTS-Glu	12.9	11.3	1.6
L-glutamic acid	1.4	0.0	1.4
L-leucine	1.5	0.0	1.5
L-phenylalanine	1.7	0.0	1.7

The OTS-amino acids catalysts were further tested for the asymmetric hydration of epoxycyclohexane. The catalysts show promising enantioselectivity with 10–18% ee (*S*) for (*1S,2S*)-*trans*-1,2-cyclohexanediol and (*1R,2R*)-*trans*-1,2-cyclohexanediol (see Figure 4.13). Figures 4.14 shows the gas chromatograms of the (*1R,2R*)-*trans*-1,2-cyclohexanediol, (*1S,2S*)-*trans*-1,2-cyclohexanediol and the mixture of (*1R,2R*)-*trans*-1,2-cyclohexanediol and (*1S,2S*)-*trans*-1,2-cyclohexanediol after hydration of epoxycyclohexane by using OTS-Glu as a catalyst.

As shown in Figure. 4.13, OTS-Glu catalyst show the highest enantioselectivity with 18% ee (*S*) for (*1S,2S*)-*trans*-1,2-cyclohexanediol and (*1R,2R*)-*trans*-1,2-cyclohexanediol, while pure L-amino acids possess no enantioselectivity. This phenomenon could be explained that pure L-amino acids do not possess function as chiral promoter, while the OTS-amino acids catalysts show enantioselectivity. This suggests that hydrolyzed OTS bonded with L-amino acids.

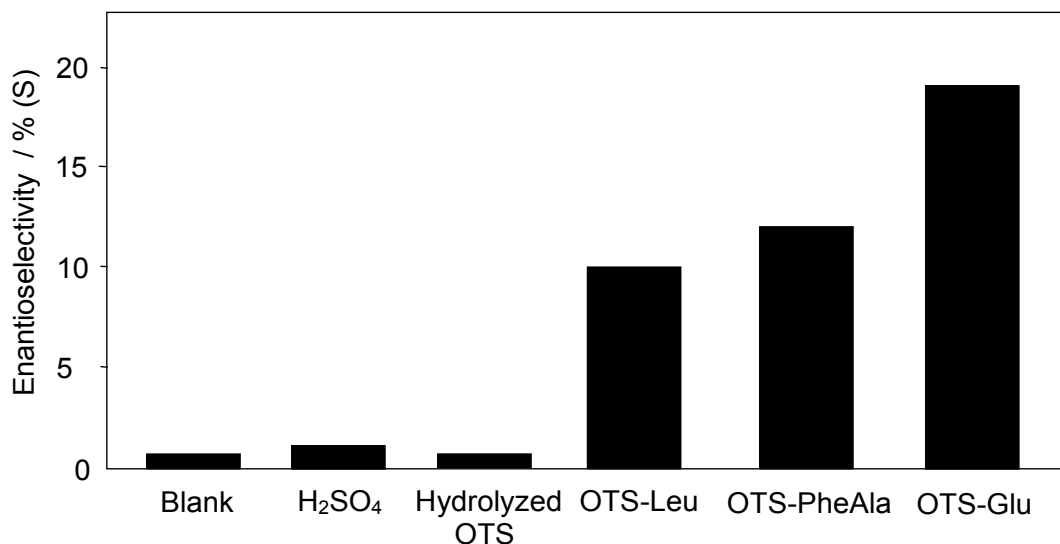


Figure 4.13: Enantioselectivity of hydration of epoxycyclohexane by hydrolyzed OTS-amino acids.

Considering that the amino acids are the integral part of the catalysts, the lower enantioselectivity of OTS-PheAla and OTS-Leu catalysts compared to that of OTS-Glu catalyst may be due to the different structure of the amino acid in the three samples. It may be suggested that the enhanced catalytic activity of the hydrolyzed OTS-amino acids is mainly caused by the specific adsorption and physical properties of the catalysts with the amino acid as a chiral promoter. This argument is supported by the fact that the increase in enantioselectivity with the decrease in hydrophathy index as shown in 4.14.

The alternative explanation for the different enantioselectivity of the three tested amino acids is that L-glutamic acid contains an additional carboxyl group available for hydrogen bonding which can definitely contribute to the larger enantioselectivity in the non-covalent catalysis.

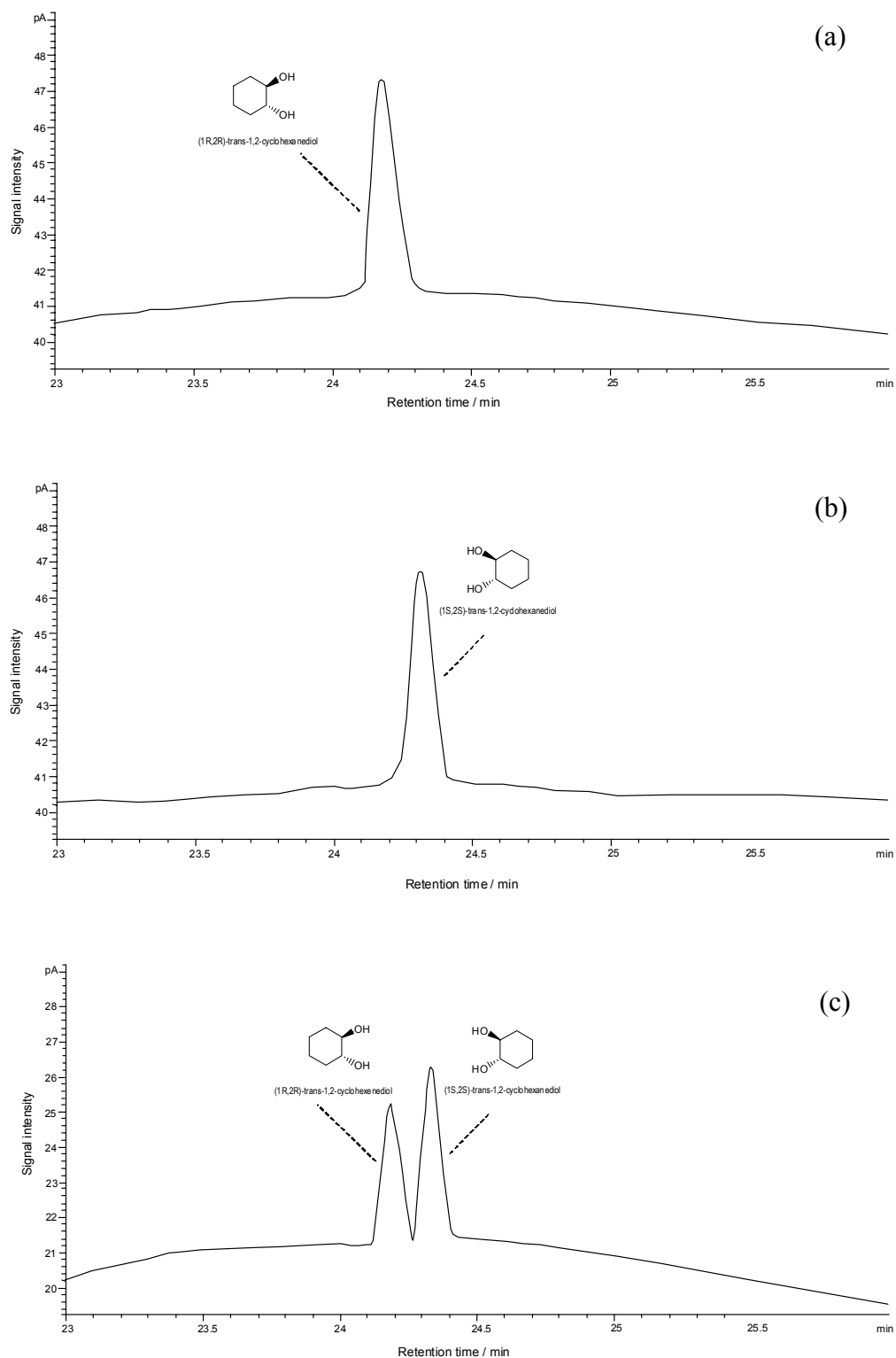


Figure 4.14: Gas chromatograms of (a) (1R,2R)-trans-1,2-cyclohexanediol, (b) (1S,2S)-trans-1,2-cyclohexanediol and (c) (1R,2R)-trans-1,2-cyclohexanediol and (1S,2S)-trans-1,2-cyclohexanediol after hydration of epoxycyclohexane by using OTS-Glu as a catalyst.

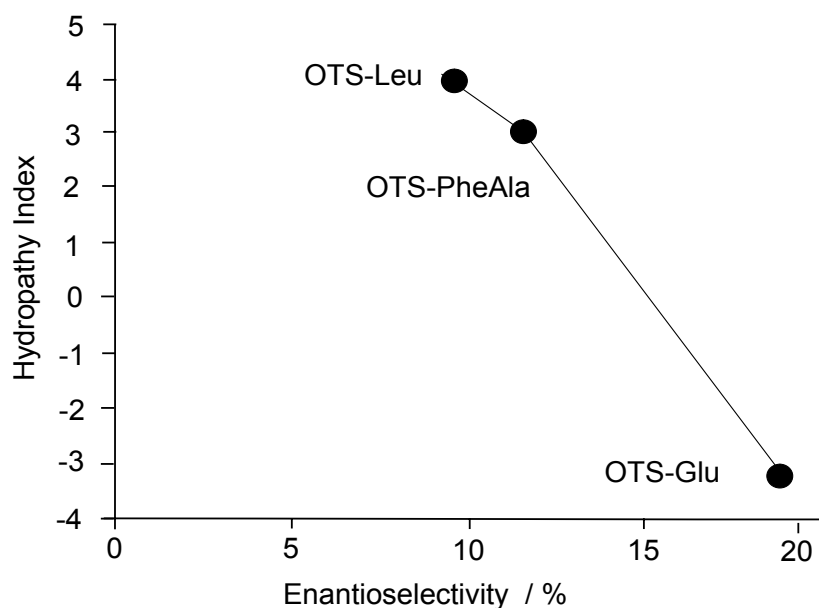


Figure 4.15: Hydrophilicity effects on enantioselectivity.

It was demonstrated in section 4.2. that during the reaction, under stirring condition, an abrupt visual homogenization was observed and this suggested the formation of the emulsion in the presence of the solid particles (see Figures 4.2 and 4.3). A catalyst that possesses both hydrophobic and hydrophilic components exhibits amphiphilic character. The flexibility of the hydrophobic octadecyl groups allows the formation of micellar aggregates in the system containing immiscible organic and aqueous phases. Figure 4.15 shows that when the hydrophilicity of the OTS-amino acids increases, the enantioselectivity increases.

On the basis of the above discussion, the possible explanation for the enhancement of catalytic activity of the amphiphilic chiral solid catalyst can be considered by the formation of “chiral pool” for enantioselective hydration of epoxycyclohexene. The chiral pool shown in Figure 4.16 absorbed H^+ and thus induced the enantioselectivity in the presence of amino acid as a chiral promoter. The effect of hydrophobicity in enantioselectivity of the catalyst in hydration of epoxycyclohexene is observed in the comparisons of hydrophobicity of the amino acids.

It is expected that the hydrophilic micro domains in micellar aggregates will act as “chiral pool” for acid chiral reaction. The reactivity for OTS-amino acids catalysts is higher than the pure amino acids as shown in Table 4.3. This suggests that the “chiral pool” formed by the hydrolyzed OTS-amino acids enhances higher reactivity than those of pure amino acids although both have equal quantity of acids in the reaction. However, the enantioselectivity, although not yet high enough, demonstrates the possibility to synthesize a new kind of chiral solid catalysts for potential applications in asymmetric reactions.

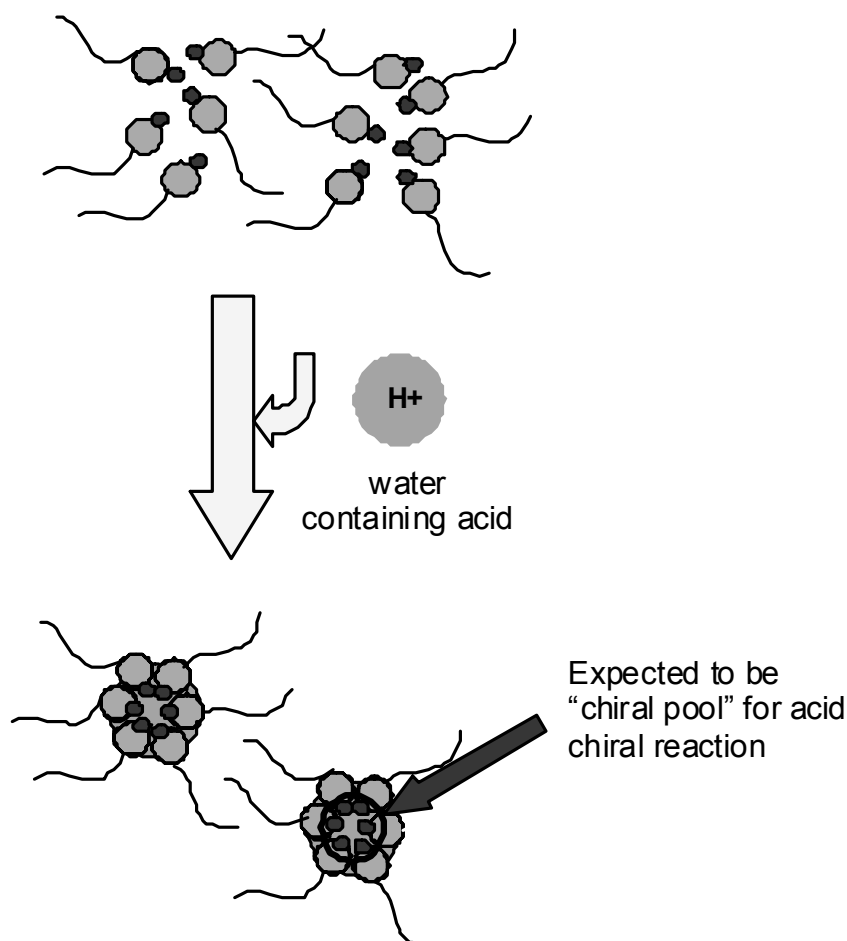


Figure 4.16: Amphiphilic chiral solid catalyst as heterogeneous micellar catalyst in enantioselective hydration of epoxycyclohexene.

CHAPTER V

CONCLUSIONS

In this study, we have studied the physicochemical and catalytic properties of heterogeneous asymmetric catalyst. The catalysts were synthesized using amino acid as chiral promoter by attachment of amino acid such as L-glutamic acid, L-leucine and L-phenylalanine to the hydrophilic part of hydrolyzed octadecyltrichlorosilane (OTS). The results obtained from the study have proven that heterogeneous catalyst possesses enantioselectivity in the hydration of epoxycyclohexane. We have demonstrated that amino acids attached on the hydrolyzed OTS induced the enantioselectivity of the hydration reaction.

The catalytic potential of heterogeneous asymmetric catalysts for enantioselective reactions is demonstrated in the hydration of epoxycyclohexane. All OTS-amino acids show promising enantioselectivity with 10-18% ee (*S*) for (1*S*,2*S*)-*trans*-1,2-cyclohexanediol and (1*R*,2*R*)-*trans*-1,2-cyclohexanediol, while pure L-amino acids possess no enantioselectivity. The enhanced catalytic activity of the hydrolyzed OTS-amino acids compared to pure amino acids is proposed as the effect of the specific adsorption on the chiral pool of the catalysts with amino acid as a chiral promoter which serves as a more reactive reaction media compared to those of pure amino acids.

Although the selectivity of the OTS-amino acids is almost similar (10-19%) ee excess in (1*S*,2*S*)-*trans*-1,2-cyclohexanediol, the degree of selectivity was found

to be increased when the hydrophilicity of the OTS-amino acids catalyst increase in order of: L-leucine < L-phenylalanine < L-glutamic acid.

Finally, it is concluded that the enantioselectivity of heterogeneous asymmetric catalyst using amino acid as chiral promoter is possible. Although not yet high enough in terms of selectivity and activity, it demonstrates the possibility to synthesize a new kind of chiral solid catalysts for potential applications in asymmetric reactions for producing enantiopure compounds.

REFERENCES

1. Collins, A. N., Sheldrake, G. N. and Crosby, J. *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds*. John Wiley & Sons, Ltd, Chichester. 1992.
2. Collins, A.N., Sheldrake, G. N. and Crosby, J. *Chirality in Industry II: Developments in the Commercial Manufacture and Applications of Optically Active Compounds*. John Wiley & Sons, Ltd, Chichester. 1997.
3. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*. Wiley - Interscience, New York. 1994.
4. Doyle, M. *Advances in Catalytic Processes: Asymmetric Chemical Transformations*. Vol. 1, JAI, Greenwich. 1995.
5. Jacobsen, E.N., Pfaltz, A. and Yamamoto, H. *Comprehensive Asymmetric Catalysis*. Vol. I – III, Springer, Berlin. 1999.
6. Brunner, H. and Zettlmeier, W. *Handbook of Enantioselective Catalysis*. Vol. 1 –2, Wiley - VCH Verlag GmbH, New York. 1993.
7. Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd editions, Wiley - VCH Verlag GmbH, New York. 2000.
8. Hazen, R. M. and Sholl, D. S. Chiral Selection on Inorganic Crystalline Surfaces. *Nature Materials*. 2003. 2: 367-374.
9. Cahn, R. S., Ingold, C.K. and Prelog. V. The Specification of Asymmetric Configuration in Organic Chemistry. *Experientia*. 1956. 12: 81-89.
10. Cahn, R. S., Ingold, C. K. and Prelog. V. Specification of Molecular Chirality. 1966. *Angew. Chem. Int. Ed.* 5: 385-415.
11. Simmons, B.R., Lush, R. M. and Figg, W. D. A Reversed-Phase High Performance Liquid Chromatography Method Using Solid Phase Extraction to Quantitate Thalidomide in Human Serum. 1997. *Anal. Chim. Acta*. 339: 91-97.
12. Aboul-Enein H. Y. and Wainer, I. W. *The Impact of Stereochemistry on Drug Development and Use*. Wiley, New York. 1997.
13. Caldwell, J. Stereochemical Determinants of the Nature and Consequences of Drug Metabolism. 1995. *J. Chromatography A*. 694: 39–48.

14. Caldwell, J. Importance of Stereospecific Bioanalytical Monitoring in Drug Development. 1996. *J. Chromatography A*. 719: 3-13.
15. Wainer, W. *Drug Stereochemistry: Analytical Methods and Pharmacology*. Second Editions. Marcel Dekker, New York. 1993.
16. Tucker, G. T. and Lennard, M. S. Enantiomer Specific Pharmacokinetics, *Pharmacol. Ther.* 1990. 45: 309-329.
17. F. Jamali, R. Mehvar, and F. M. Pasutto, Stereospecific Aspects of Drug Action and Disposition: Therapeutic Pitfalls. *J. Pharm. Sci.* 1989. 78: 695-715.
18. Drayer, D. E. Pharmacodynamic and Pharmacokinetic Differences Between Drug Enantiomers in Humans: An overview. *Clin. Pharmacol. Ther.* 1986, 40: 125-133.
19. Williams, K. and Lee, E. Importance of Drug Enantiomers in Clinical Pharmacology. *Drug.* 1985. 30: 333-354.
20. Ariëns, E. J. Stereochemistry, A Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical. *Eur. J. Clin. Pharmacol.* 1984. 26: 663-668.
21. Bielory, L. and Leonov, A. Stereoconfiguration of Antiallergic and Immunologic Drugs. *Ann. Allergy Asthma Immunol.* 2008. 100: 1-9.
22. Federsel, H.-J. Asymmetry on Large Scale: The Roadmap to Stereoselective Processes. *Nat. Rev. Drug Discov.* 2005. 4: 685-697.
23. De Camp, W. H. The FDA Perspective on The Development of Stereoisomers *Chirality*. 1989. 1: 2-6.
24. Stephens. T. Reinventing Thalidomide - Despite Its Notorious History, Thalidomide is Becoming an Important Treatment for Leprosy, Aids and Cancer. *Chem. in Britain*. 2001. 37: 38-40
25. Sheldon. R.A. *Chirotechnology. Industrial Synthesis of Optically Active Compounds*. Marcel Dekker, New York. 1993.
26. Baiker. A. Transition State Analogues — A Guide for the Rational Design of Enantioselective Heterogeneous Hydrogenation Catalysts. *J. Mol. Catal. A*. 2000 163: 205–220.
27. Gellman, A. J. Chiral Surfaces: Accomplishments and Challenges. *ACS Nano*, 2010. 4: 5–10.
28. Spelberg, L. Enantioselective Biocatalytic Conversions of Epoxides. PhD thesis. Rijksuniversiteit Groningen. 2003.

29. ChiralSolv. Chiral Technologies and ChiroSolv™. Retrieved on September 1, 2010, from <http://www.chirosolve.com/>
30. Blaser, H. U., Pugin, B. and Studer, M. Enantioselective Heterogeneous Catalysis: Academic and Industrial Challenges. In De Vos, D. E., Vanketecom, I. F. J. and Jacobs, P. A. (Eds.). *Chiral Catalyst Immobilization and Recycling*. Wiley - VCH Verlag GmbH, New York. 2000.
31. Hagen, J. *Industrial Catalysis: A Practical Approach*. Wiley, Weinheim. 2006
32. McMorn, P. and Hutchings, G. J. Heterogeneous Enantioselective Catalysts Strategies for The Immobilization of Homogeneous Catalysts. *Chem. Soc. Rev.* 2003. 33:108–122.
33. Schwab, G. M. and Rudolph, L. Catalytic Cleavage of Racemates By D- and L-Quartz. *Naturwissenschaften*. 1932. 20: 363–364.
34. David S. Sholl, D.S. and Gellman, A. J. Developing Chiral Surfaces for Enantioselective Chemical Processing. *AIChE Journal*. 2009. 55: 2484–2490.
35. Davies, N. M., and Teng, X. W. Importance of Chirality in Drug Therapy and Pharmacy Practice: Implications for Psychiatry. *Adv. Pharmacy*. 2003. 1: 242-252.
36. Hutchings, G. C. Heterogeneous Asymmetric Catalysts: Strategies for Achieving High Enantioselection. *Ann. Rev. Mater Res.* 2005. 35: 143-166.
37. Wells, P. B. and Wilkinson, A. G. Platinum Group Metals As Heterogeneous Enantioselective Catalysts. *Top. Catal.* 1998. 5: 39–50.
38. Von Arx, M., Mallat, T. and Baiker, A. Asymmetric Hydrogenation of Activated Ketones on Platinum: Relevant And Spectator Species. *Top. Catal.* 2002. 19: 75–87.
39. Kukula, P. and Cervený, L. Effects of Reaction Variables on Enantioselectivity of Modified Raney Nickel Catalyst. *J. Mol. Catal. A*. 2002. 185: 195–202.
40. Sugimura, T., Nakayama, S. And Tai, A. Over 98% Optical Yield Achieved by A Heterogeneous Catalysis. Substrate Design and Analysis of Enantio-Differentiating Factors of Tartaric Acid-Modified Raney Nickel Hydrogenation. *Bull. Chem. Soc. Jpn.* 2002. 75: 355–363.
41. Osawa, T., Sakai, S., Harada, T. and Takayasu, O. Highly Durable Enantio-Differentiating Nickel Catalyst for Repeated Use for the Hydrogenation of Methyl Acetoacetate. *Chem. Lett.* 2001. 30: 392-393.

42. Davis, M. E. and Lobo, R. F. Zeolite and Molecular-Sieve Synthesis, 1992. *Chem. Mater*, 4: 756-768.
43. Lobo, R. F., Zones, S. I. and Davis, M. E. Effect of the Stacking Probability on the Properties of the Molecular Sieve CIT-1, SSZ-26 and SSZ-33, 1994. *Stud. Surf. Sci. Catal.* 84: 461.
44. Barrett, G. C. and Elmore, D. T. *Amino Acids and Peptides*. Cambridge University Press, 1998.
45. Stryer, L., Berg, J. M. and Tymoczko, J. L. *Biochemistry*. San Francisco: W.H. Freeman. 2002.
46. Samsonov, S. A. Protein-Protein Interactions: Impact of Solvent and Effects Of Fluorination. Ph.D. Thesis. Technical University of Dresden. 2009.
47. Monastiriotis, S. *Octadecyltrichlorosilane (OTS) Partial Monolayers OTS - Aminophenyltrimethoxysilane (APhMS) Mixed Monolayers*. City College of New York. 2005.
48. Feibush, B., Woolley, C. L. and Mani, V. Separation of Chiral Silicon Compounds Using Permethylated α -, β -, and γ -Cyclodextrin Capillary GC Columns. *Anal. Chem.* 1993. 65: 1130–1133.
49. Supelco, Chiral Cyclodextrin Capillary GC Columns. Bulletin 877.
50. Feng, X., Fryxell, G. E., Wang, L.Q., Kim, A.Y., Liu, J. Organic Monolayers on Ordered Mesoporous Supports. 1997. *Science*. 276: 923-926.
51. Liu, J., Feng, X., Fryxell, G. E., Wang, L.Q., Kim, A. Y. and Gong. Hybrid Mesoporous Materials with Functionalized Monolayers. *Adv. Mater.* 1998. 10: 161-165.
52. Kyte, J. and Doolittle, R.F. A Simple Method for Displaying the Hydropathic Character of a Protein. 1982. *J. Mol. Biol.* 157: 105-132.