School of Chemistry

University of St Andrews

Inorganic-Organic Hybrids: Novel Molecular Sieves with Potential Applications in Asymmetric Catalysis.

Thesis submitted for the degree of Doctor in Philosophy.

Eirene Kirton

January 2002

Th

E150

Declaration

(i) I, Eirene Helen Margaret Kirton, hereby certify that this thesis, which is approximately 41 000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

date 20/5/02 signature of candidate

(ii) I was admitted as a research student in October 1998 and as a candidate for the degree of Doctor of Philosophy in October 1999; the higher study for which this is a record was carried out in the University of St Andrews between 1998 and 2001.

date 20/5/02 signature of candidate

(iii) I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of Doctor of Philosophy in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

date 1/5/02 signature of supervisor

date 20 May 02 signature of supervisor

Copyright

In submitting this thesis to the University of St Andrews I wish access to it to be subject to the following conditions:

for a period of 5 years from the date of submission, the thesis shall be withheld from use;

I understand, however, that the title and abstract of the thesis will be published during this period of restricted access; and that after the expiry of this period the thesis will be made available for use in accordance with the regulations of the University for the time being in force, subject to any copyright in the work not being affected thereby, and a copy of the work may be made and supplied to any *bona fide* library or research worker.

date 20/5/02 signature of candidate .

Content

Abstract

This thesis concerns the preparation, characterisation and potential applications in asymmetric catalysis of inorganic – organic hybids based on MCM-41 and silica.

MCM-41 is a mesoporous silica with a hexagonal array of pore with a diameter of approximately 30 Å. The preparation of such materials, by a template method using a suitable surfactant and sodium silicate solution, plus their subsequent characterisation has been successfully completed. MCM-41 was further modified to produce the inorganic – organic hybrids. The preparation and characterisation of both amino acid and amino acid derivative supported materials will be discussed and have been tethered to silica and MCM-41.

Three main areas of asymmetric synthesis have been studied. The first concerns asymmetric epoxidation of α,β unsaturated ketones in the presence of amino acids. Amino acids and peptides were supported on MCM-41 and silica and have been tested for asymmetric induction of the epoxidation of chalcone with urea hydrogen peroxide. Silica supported amino acids have also been investigated as potential catalysts for ring cyclisation of epoxy alcohols. These materials were investigated for their effect on enantioselectivity of the cyclisation reaction. The final area that was investigated was the asymmetric reduction of imines and ketones with oxazaborolidines. Mechanistic studies of the solution phase asymmetric reductions of imines with methyl CBS oxazaborolidine and other oxazaborolidines have been achieved. Investigation of the effect of supporting oxazaborolidines on silica and MCM-41 on imine and ketone reductions has been accomplished.

Acknowledgements

I would like to thank my three supervisors for all their help and encouragement throughout my Ph.D.; Professor Robert Field, for all his help with the organic chemistry side of my project. To Professor Russell Morris for his help in the inorganic chemistry side of my project and, finally, to Dr. Gary Tughan for the ongoing encouragement and for his help while I was at GSK.

I would also wish to thank all the technical staff at the University of St Andrews and University of East Anglia, for their help in running analysis, preparation of glassware and repairs of equipment. Thanks must also go to Professor Field's group, especially Ravi for his assistance and encouragement in the lab. Thanks also to everyone at GSK (Stevenage) for making me feel welcome and for their support while I was there.

This project would have not been possible without funding from the EPSRC and GlaxoSmithKline.

We wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.

Last but not least, thanks must go to my parents, for their love and support throughout the years. Without it, I would not be where I am today.

Abbreviations

Al-MCM-41	Aluminum modified MCM-41
Chalcone	1,3-Diphenylpropen-1-one
CSA	Camphor Sulfonic Acid
CSP	Chiral stationary phases
CTAB	Cetyltrimethylammonium bromide
d.e.	Diastereomeric excess
DHQ	1,4-Bis (9-*O*-dihydroquinine)
DHQD	1,4-Bis(9-*O*-dihydroquinidine)
$DHQD_2PHAL$	1,4-Bis(9-*O*-dihydroquinidine)phthlalazine
$DHQD_2PY$	1,4-Bis(9-*O*-dihydroquinidine)pyridazine
DIEA	Diisopropylethylamine
DNB	Dinitrobenzamide
e.e.	Enantiomeric excess
Eq.	Equivalents
HEMA	2-Hydroxyethyl methacrylate
IBCF	Isobutylchloroformate
MCM	Mobil Composites of Matter
MeO-PEG	Poly (ethylene glycol) methoxy ether
MMA	Methyl methacrylate
NCA	*N*-Carboxy anhydride
NMM	*N*-Methylmorpholine
PDL	Poly-D-leucine
PEG	Poly(ethylene glycol)
Pfp	Pentafluorophenyl

PLL	Poly-L-leucine
PMA	PhosphoMolybdic Acid
OPfp	Pentafluorophenoxy
Oxone®	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
Salen	*N*, *N'*-Bis (salicylidene) ethylenediamine dianion
TBHP	^{t}Butyl hydroperoxide
UHP	Urea hydrogen peroxide complex
XRD	X-ray diffraction

Chapter 1

Introduction to Mesoporous Molecular Sieves - MCM-41.

1.1 General Background to Molecular Sieves and Asymmetric Synthesis.

For many years, the petroleum industry has widely used molecular sieves for cracking crude oil. These molecular sieves are now becoming important to the fine chemicals industry.[1,2] On an industrial scale corrosive acids and oxidants can cause handling problems and microporous molecular sieves, acting as solid acids and shape selective catalysts, can replace these reagents and are much safer. However, in many of these applications the size of the substrate is limited by the diameter of the pore (~ 5 Å). This is where mesoporous molecular sieves may have an advantage with pore diameters ranging from 15 to 100 Å. With these pore diameters, the pores are large enough to incorporate a catalyst and the substrate. This has potential applications in asymmetric synthesis if the catalyst is chiral.

Asymmetric synthesises are important in industry because, although 25 % of drugs on the market are racemates or mixtures of diastereoisomers, there is increasing pressure for pharmaceutical companies to prepare them in homochiral form.[3,4] The problem of releasing the racemic drug is that the enantiomers can have very different physiological activities.[5] Most biological systems are chiral, so the interaction of one enantiomer with the system will be different to the interaction of the other enantiomer. This was highlighted with racemic thalidomide; one enantiomer reduced the effects of morning sickness whilst the other caused deformities in unborn babies.[6] Consequently, a cost-effective synthesis of a single enantiomer is one of the major chemical challenges faced by the pharmaceutical industry at the present time.[7] Therefore, the synthesis of a single enantiomer is an important consideration in designing new synthetic routes.[8] The problem is increased as many drugs have more than one stereogenic centre, all of which have to be controlled.[9] Another

consideration is that it is time consuming and costly for pharmaceutical companies to justify the release of a racemic drug.[3,4]

1.2 Mesoporous Materials

Molecular sieves are porous material and are classed in respect of their pore size and structure. For recent reviews on mesoporous molecular sieves, see "Studies in Surface Science and Catalysis".[10,11] Mesoporous molecular sieves have pore diameters ranging from 15 – 100Å and therefore have a large internal surface area (> 1000 m^2 g^{-1}). This allows a higher loading of catalyst to be tethered to the surface and still leave sufficient room for substrate to diffuse into the pores. Mesoporous molecular sieves can be synthesised from a variety of precursors; the most common mesoporous molecular sieves are silicates. Hydrothermal synthesis is a common synthetic method for the preparation of these types of molecular sieves. This method uses an organic molecule, typically a surfactant, as a template and structure-directing agent.[1] The template must have intermediate interactions with the solvent and the framework atoms so it can be easily removed at the end of the synthesis. The inside of the pore can then be modified, hence tuning the properties of the molecular sieve. The mesoporous silicate studied herein is MCM-41.[1]

1.3 MCM-41

MCM-41 is composed of amorphous walls (no regular structure) of silica with a regular hexagonal array of pores. The pore diameter can be controlled, within a few Å, by the surfactant used, and in the case of MCM-41 it is approximately 30Å.[1,12] MCM-41 is prepared by a hydrothermal reaction using cetyltrimethylammonium bromide (CTAB) as the template. Many mechanisms have been proposed for the synthesis of MCM-41.[13] The most common mechanism quoted is that the CTAB

forms micellular rods **(Figure 1 a)**, the silicate is attracted to the hydrophilic heads and coats the micellular rods **(Figure 1 b)**. The rods then pack together in a hexagonal array, as they come together the silicate reacts together **(Figure 1 c and d)**. Drying and subsequent calcination at 550°C, to burn off all the organic material, leaves a hexagonal array of pores **(Figure 1 e).**[13]

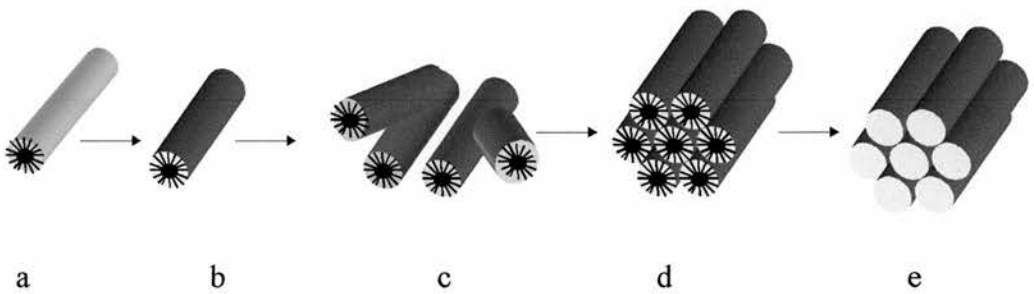


Figure 1 – Possible Mechanism for the Synthesis of MCM-41.[13]

An alternative mechanism is that a liquid crystal forms first and the surfactant aggregates around this, but this is unlikely as the concentration of the surfactant is too low to forms micellular rods.[13] Another mechanism proposed involves a layered intermediate which collapses to the hexagonal array of pores.[13] In this case, the silicate forms layers with the micellular rods in between the layers. Either charge balance or the layers puckering gives rise to the hexagonal array of linear pores.

Figure 2 shows a literature example of the XRD of MCM-41. The crystallinity slightly decreases when the template is removed during calcination, but the hexagonal array is still clearly visible; this will be discussed in chapter 2.

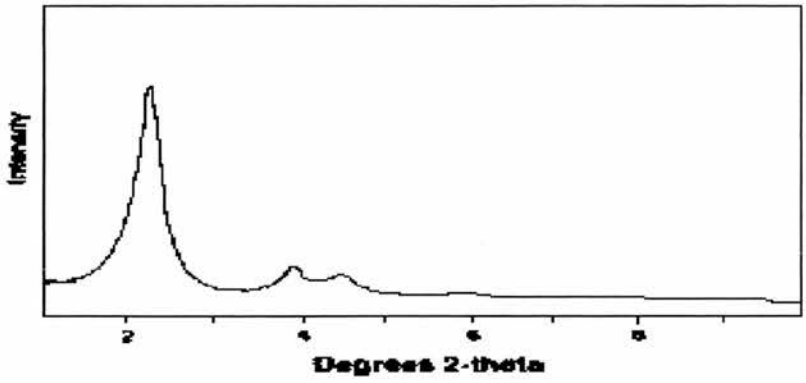


Figure 2 – Typical XRD of MCM-41.[1]

The shrinkage of the pores can be minimised by using ozone to remove the surfactant.[14] This method is very simple with the MCM-41 placed under an UV lamp with a wavelength known to create ozone from molecular oxygen. Another advantage is that the removal of the surfactant is carried out at room temperature instead of 550 °C. This research is still in its preliminary stages but could prove a more cost-effective than calcination. However, there are concerns of safety. The fate of the nitrogen and bromine of the surfactant, when treated with ozone, is unknown.[14]

MCM-41 is only slightly less thermodynamically stable than amorphous silica[13] but has lower hydrothermal stability.[15] MCM-41 is stable up to 500°C in a steam flow at atmospheric pressure whereas if there is no water present then it can be heated to 850°C before loss of structure occurs. The stability can be improved if certain cations, for example aluminium or titanium, are introduced into the hydrothermal gel. The increase in stability appears to come from the formation of thicker walls under these conditions.

1.4 Modification and Functionalisation of MCM-41.

There has been much research into the modification of MCM-41 because it has attractive structural properties of a rigid scaffold. Furthermore, most reactions will not proceed with just a silicate surface, a catalyst or reagent is required. Therefore metals have been incorporated into the silica walls or organic moieties have been tethered onto the pore surface. Both of these approaches will be discussed in turn,

1.4.1 Modification of MCM-41 with Metals

The most common metal that has been incorporated into the walls of MCM-41 is aluminium (Al-MCM-41). MCM-41 is not acidic enough for cracking processes compared to industrial zeolites (e.g.ZSM-5), but the acidity can be increased by the incorporation of aluminium species into the mesopore wall.[10,11] Aluminium can be added during the hydrothermal gel synthesis to obtain direct incorporation into the walls. This has been found to cause deterioration in the structural integrity of the resulting solid and the strength of the resulting acid is low.[10] Alternatively, aluminium can be grafted onto the pore surface after the MCM-41 has been formed. One such method uses aluminium chlorohydrate, which introduces aluminium polycations into MCM-41.[11] This enhances the acidity of the resulting molecular sieve.

There are many metal catalysed reactions that can occur inside modified MCM-41 however, the corresponding microporous zeolites tend to give better results for a specific reaction. For example, the hydroxylation of benzene to phenol can be catalysed by MCM-41which has modified with either Ti, V, Cr, Mo or Mn, but HMS (zeolite) gives superior results.[13]

1.4.2 Organic Functionalisation of MCM-41.

To modify MCM-41 with a specific organic group, a linker must first be attached to the pore surface. The three main methods for achieving this are grafting, surface chlorination followed by displacement, and post-modification **(Figure 3)**.[16]

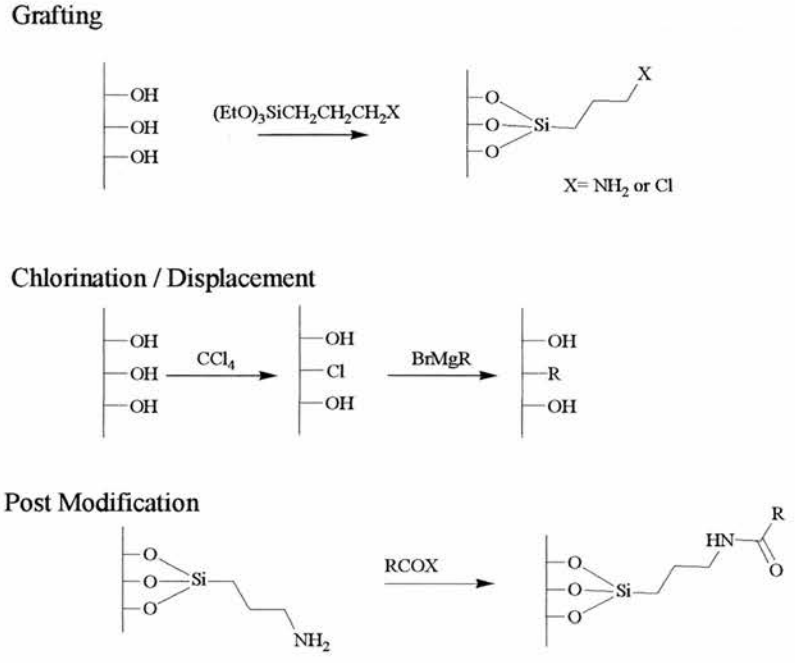


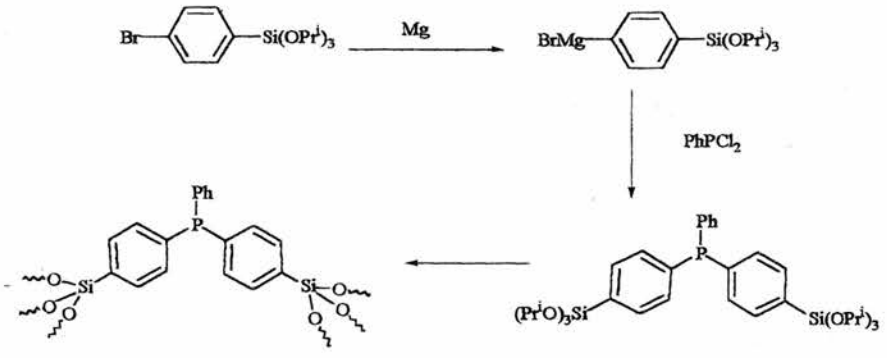
Figure 3 - Methods of Modifying Mesoporous Silicate.[16]

Grafting is the simplest and most commonly used method where the organic moiety is bound to the surface via a silane.[16] The problem with this method is that a range of surface species can be formed, and it gives a low loading of the immobilised moiety compared to the other methods.

Unlike grafting, surface chlorination precludes the formation of variable surface species.[16] Subsequent displacement reaction with a Grignard reagent forms Si-C bonds directly. Although this method produces more robust products than grafting, the R group that can be used is restricted because a strong nucleophile is required.

Post modification is used to modify functional groups introduced by the above two methods.[16] For example, an acid chloride can be reacted with an amine introduced by the grafting method to tether a catalyst via an amide linkage.

Alternatively, a less popular method to prepare organically modified mesoporous materials is to directly use the functionalised silane in the hydrothermal reaction mixture.[17] This gives higher loading than the grafting method but there is no control over where the silane is introduced and there would be some silane attached on the external surface of the particle. This could be disadvantageous if the catalyst on the external surface was not selective. One example of this is to produce inorganic-organic hybrids containing phosphorus **(Scheme 1)**. In this case, an xerogel (a porous glass prepared usually from a sol-gel method) was formed and further work is need to explore this new material's applications.



Scheme 1 – Synthesis Of Inorganic-Organic Hybrids Containing Phosphorus.[17]

1.5 Literature Examples Of Synthetic Reactions Using Modified Mesoporous Solids.

Although much research has been carried out by Mobil researchers, no commercial use of MCM-41 for cracking has been established.[13] There has also been a large amount of research on placing metals into MCM-41.

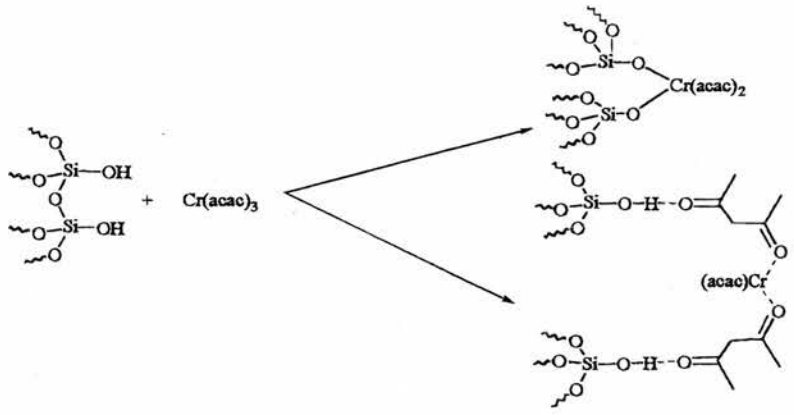
1.5.1 Direct Grafting of Metals onto Mesoporous Molecular Sieves.

Al-MCM-41 can be used for acid-catalysed reactions, and as with MCM-41 it has no commercial use.[13] Although it is useful for the cracking of larger substrates like gasoil, zeolites are still used industrially. One example for the use of Al-MCM-41 is the conversion of low-density polythene to hydrocarbon feedstock. From table 1 Al-MCM-41 gives better results than amorphous aluminosilicates but ZSM-5 (microporous molecular sieve) still gives the best results. ZSM-5 is the only catalyst that will give the same % mass conversion with the higher plastic/ catalyst mass ratio. The other two catalysts give the best results with a plastic to catalyst mass ratio of 4 and at this ratio Al-MCM-41 gives comparable results to ZSM-5. Aluminosilicates gives a much lower % mass conversion. ZSM-5 is probably efficient because the pores are more acidic.[18]

Catalyst	**Aluminosilicate**		**Al-MCM-41**		**ZSM-5**	
Plastic/ cat. mass ratio	18	4	18	4	18	4
Conversion (mass %)	5.11	35.18	62.83	95.87	95.40	94.32

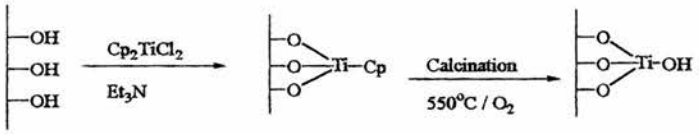
Table 1 – Cracking of Low Density Polythene over Al-MCM-41, Aluminosilicates and ZSM-5.[18]

Chromium has been directly tethered to silanol groups in Al-MCM-41 but different chromium species are present on the pore surface. This type of catalyst can then used for the polymerisation of ethene **(Scheme 3)**.[19]



Scheme 2 – Direct Attachment of Chromium to AL-MCM-41.[19]

Cyclohexene can be epoxidised with titanium-doped MCM-41 and tetrabutylperoxyhydroxide.[20] The titanium was grafted to MCM-41 via titanocene (Cp_2TiCl_2), followed by calcination to remove the organics. This catalyst gave a maximum turnover frequency of 3 mmol cyclohexene per g catalyst per min. The catalyst is inactivated after ninety minutes but can be easily regenerated by calcination however, further tuning of the catalyst should increase its lifetime **(Scheme 3)**.



Scheme 3 – Titanium Bound To MCM-41.[20]

Another process utilises a molybdenum (VI) complex for the catalytic epoxidation of alkenes **(Figure 4)**.[21] In this example, the ligand on the metal is lost and the active metal species (exact structure unknown) binds to molecular sieves (the literature does not state which one). The molecular sieves also directly binds the *tert*-butyl peroxide co-substrate. However, the lifetime of this catalyst is very short. As the chiral ligand is lost during the preparation of the catalyst, there is no asymmetric induction.

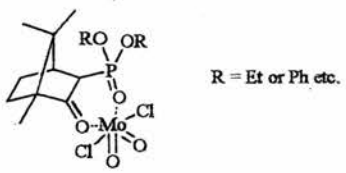
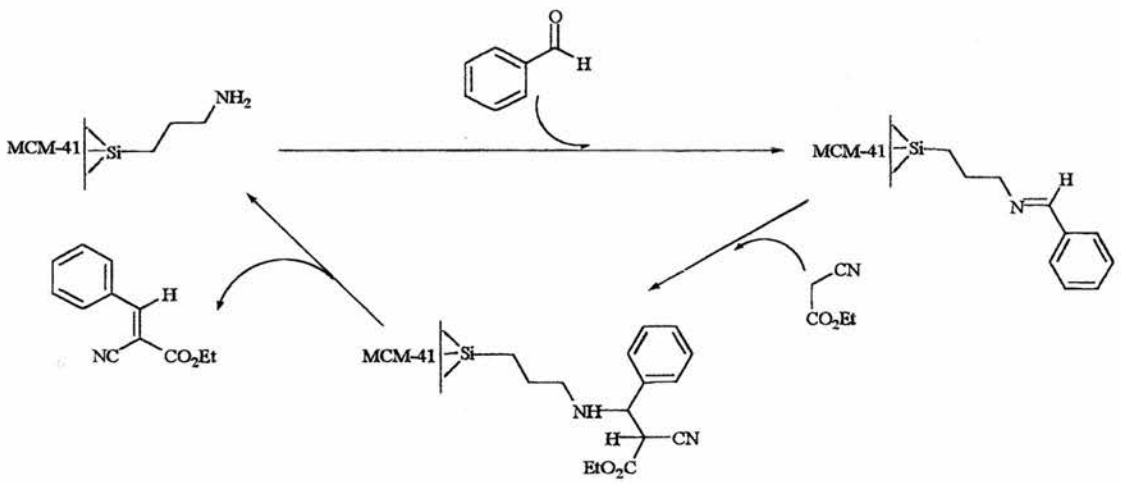


Figure 4 – Molybdenum (VI) Catalyst For Alkene Epoxidation.[21]

1.5.2 Organic Modification of Mesoporous Molecular Sieves.

1.5.2.1 Knoevenagel Condensation Reactions.

The mesoporous molecular sieve produced from the grafting of (3-aminopropyl) triethoxysilane can be used, without further modification, as a catalyst in the Knoevenagel condensation reaction.[22] The amine forms an imine with the aldehyde reactant producing a better electronic environment for the second reactant to attack **(Scheme 4)**. The rate of reaction is dependent on the amine loading.

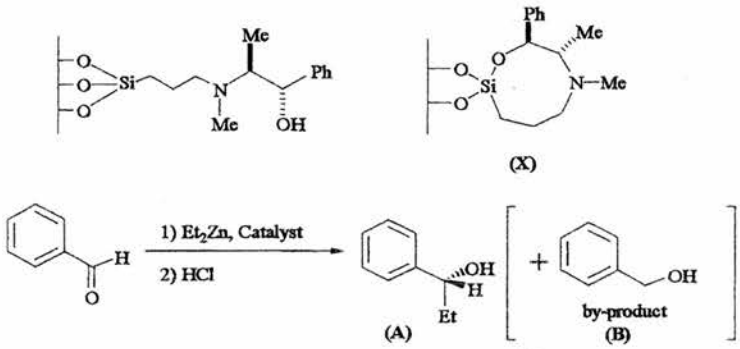


Scheme 4 – Catalysis using Modified MCM-41.[22]

1.5.2.2 Alkylation of Benzaldehyde

Chiral catalysts have also been supported on MCM-41. One illustration of this is the use of ephedrine in the alkylation of benzaldehyde **(Scheme 5)**.[23,24] The mechanism for the heterogeneous reaction and the homogeneous reaction are thought to be the same. The homogeneous reaction gives an enantiomeric excess of 67%, but this

drops to 35% when the catalyst is bound to MCM-41. The enantioselectivity drops further when the catalyst is supported on silica. Stirring has no effect on the rate nor does the concentration of $ZnEt_2$. However, the selectivity and the enantioselectivity increases as the loading of ephedrine on MCM-41 increases. One of the problems with the MCM-41 catalyst is that unreacted alkoxy groups from the grafting process can react with the bound ephedrine to form a cyclic moiety, which is inactive **(Scheme 5, structure X)**.

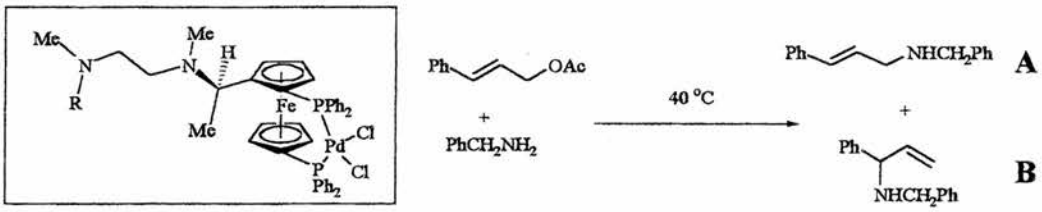


Catalyst	e.e. %	Selectivity % [A/(A+B)]
Ephedrine	67	97
MCM-41 Supported Ephedrine	37	87
Silica Supported Ephedrine	11	80

Scheme 5 - Stereoselectivity of homogeneous and immobilised Ephedrine Catalysed Benzaldehyde Alkylation. [23,24]

1.5.2.3 Allylic Substitution with MCM-41 supported palladium – ferrocenyl phosphine catalyst.

Another example is shown in **Scheme 6** using a palladium – ferrocenyl phosphine catalyst.[25] In this example, the effect of supporting the catalyst is far greater than in the ephedrine case.



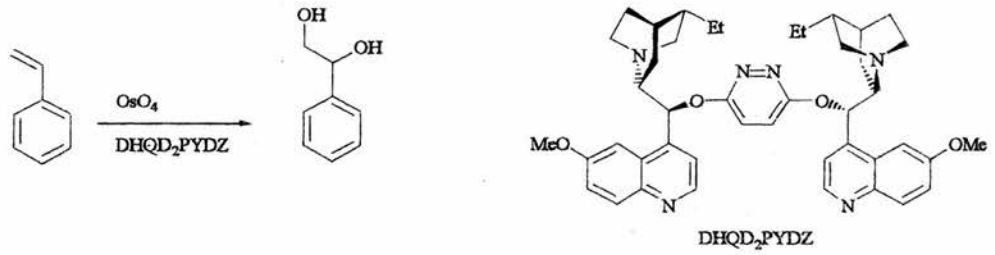
Catalyst R=	Conversion	% A	% B	% e.e. of B
H	76	> 99	0	NA
Carbosil (aminopropyl linker)	98	98	2	43
MCM-41 (aminopropyl linker)	> 99	49	51	> 99

Scheme 6 – Supported Palladium – Ferrocene Catalyst and the Catalysed Reaction.[25]

From table 6, several important points can be observed. By converting the chemical environment of the catalyst from solution onto a silicate surface changes the selectivity of the reaction. The homogeneous catalyst only produces the straight chain product **(Scheme 6 A)**. Once the catalyst is placed on the silicate then some of the chiral branched product is observed **(Scheme 6 B)**. The yield of B is larger with MCM-41 than with silica and the e.e. of B is also greater with the former (> 99 % vs. 43 %).

1.5.2.4 Dihydroxylation of alkenes.

$DHQD_2PYDZ$ and analogues are typical ligands used for the OsO_4 catalysed dihydroxylation of alkenes **(Scheme 7)**.[12, 26 - 28] This system has not been tethered on to MCM-41 but instead onto silica; however the same chemical procedures apply. Using this system in the solution phase, very high enantioselectivities can be achieved, for example, with DHQD2PYDZ, allyl 4-methoxybenzoates give the corresponding diols in 98-99% yield and e.e. of 97-99%.



Scheme 7 – Dihydroxylation of Styrene with the OsO_4 and $DHQD_2PYDZ$.[26]

When the $DHQD_2PYDZ$ system was bound to silica gel [$R=S(CH_2)_2O(CH_2)_3Silica$] **(Figure 5 A)**, only moderate enantioselectivities were obtained.[29] For example using styrene as a substrate an e.e. of 56 % was obtained. However, very good e.e's were obtained (≥ 97 %) when $DHQD_2PYDZ$ was bound symmetrically to silica gel **(Figure 5 B)**.[30] Catalyst A will have more degrees of freedom, compared to catalyst B, as it is not tethered as tightly to silica. This may explain the better results with B compared to A.

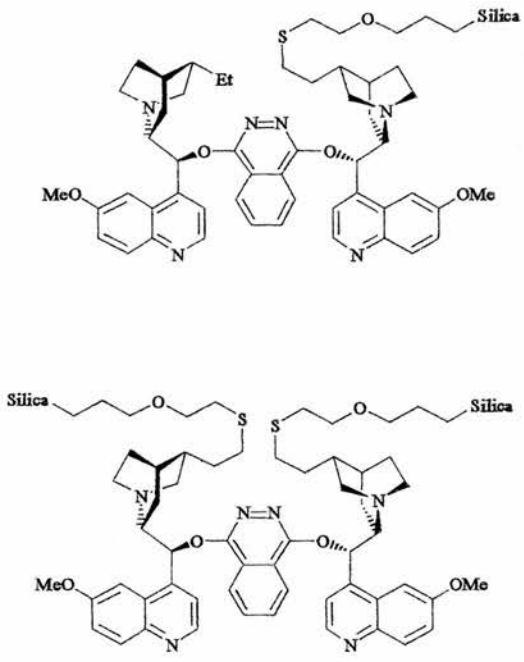
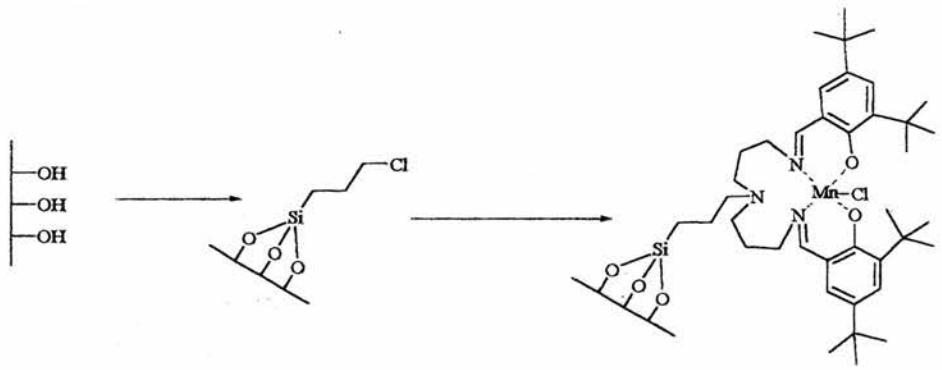


Figure 5 – Bound DHQD to Silica.[30]

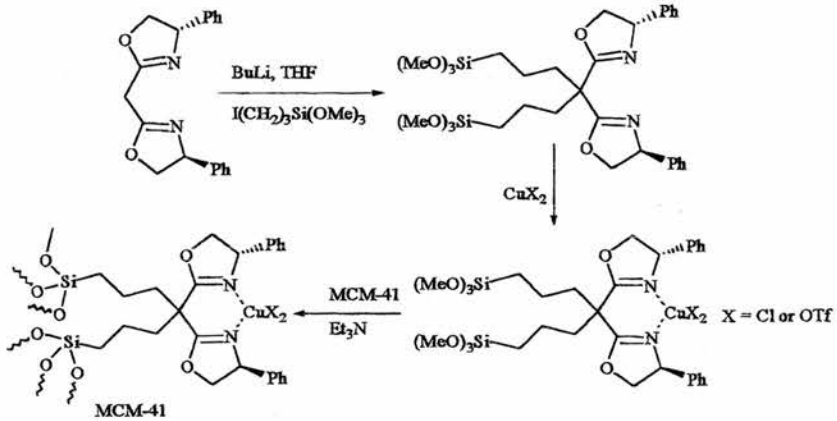
Transition metal catalysts have been tethered to MCM-41 via the ligand and then the transition metal is co-ordinated to the ligand. Asymmetric syntheses can be achieved if the ligand is chiral but examples of this are scarce. Non-chiral manganese (III) salen complexes have been successfully tethered to MCM-41 **(Scheme 8)**.[31]



Scheme 8 – Bound Mn (II) Salen Complex. [31]

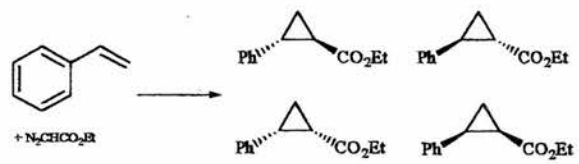
1.5.2.5 Cyclopropanation reaction with stryene and ethyl diazoacetate.

Asymmetric cyclopropanation reactions are catalysed by a copper bis(oxazoline) complexes and this catalyst has been tethered to MCM-41.[32] The catalyst is prepared by reacting the methyl bis (oxazoline) with iodopropyl trimethoxy silane thus forming another silane which can be tethered to MCM-41 **(Scheme 9)**.



Scheme 9 – Preparation of Copper bis(oxazoline) complex immobilised on MCM-41.[32]

When these catalysts were tested for the cyclopropanation of styrene, they gave comparable results to the homogeneous catalyst **(Scheme 10)**. The triflate version of the catalyst did not deactivate as fast as the chloride catalyst. The deactivation was due to by-products that complexed to the catalyst.



Catalyst	Cu (mol %)	run	Yield (%)	Trans /cis	e.e. (cis %)	e.e. (trans %)
$CuCl_2$ (homogeneous)	1	1	19.5	1.99	23	21
$Cu(OTf)_2$ (homogeneous)	1	1	46.3	2.05	49	58
MCM-41/ Cl version	0.1	1	38.7	1.89	48	54
		2	23.7	1.80	48	52
MCM-41/ OTf version	0.24	1	47.4	1.95	46	51
		2	46.6	1.78	42	45

Scheme 10 – Comparison of Homogeneous Copper bis(oxazoline) Catalysts and MCM-41 Supported Catalysts for the Cyclopropanation of Styrene.

1.6 Chiral Stationary Phases For the Resolution of Enantiomers

1.6.1 Application of Chiral Phases

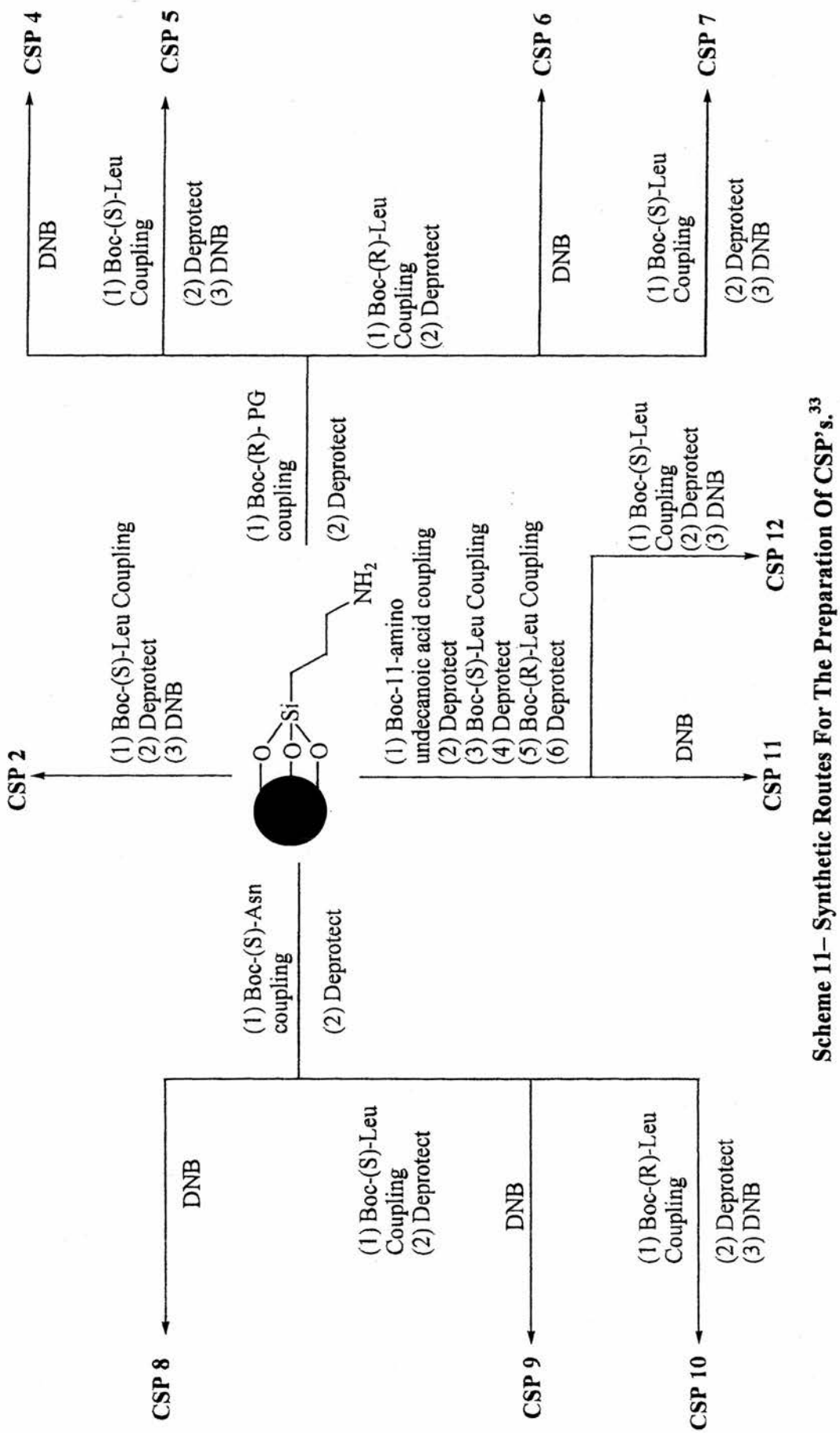
Industry requires enantioselectivities greater then 90 % to even consider an asymmetric process for further development. With methods available to date, this is not always possible and therefore the enantiomers need to be separated. Alternatively, chiral stationary phases are used to assess the enantioselectivity of a reaction under investigation. The problem in separating enantiomers is that apart from their optical activity, their physical properties are the same unless subjected to a

chiral environment. In the presence of a chiral stationary phase (CSP), one enantiomer will elute faster than the other enantiomer due to differential affinity for the CSP.[33]

1.6.2 Synthesis of Chiral Stationary Phases Based on Silica.

Amino acids have been employed in the synthesis of commercially available silica based CSP. However, new CSPs are being developed and investigated, because there are still many difficult separations to investigate. In order to assess the structural and electronic properties that produce good CSPs the investigation of new CSP has been carried out in a combinatorial fashion. Multiple parallel synthesis and screening of novel CSP has been achieved and this will be discussed later.

There are many different strategies to synthesise CSP's. Either chiral building blocks, such as amino acids, can be built up systematically or the chiral moiety can first be synthesised and then tethered to the solid support.[34,35] The former is more useful in the development of a variety of CSP's. For example, Welch and co-workers prepared a range of CSP's by the sequential addition of Boc-protected amino acids to aminopropyl functionalised silica, and once a tripeptide had been produced the *N*-terminus was capped with DNB.[33] The major disadvantage of this method is the problem with incomplete reaction on the solid support. Nevertheless this can be minimised and is an attractive procedure to produce a variety of CSP's. The various routes to synthesise the CSP's are shown in Scheme 11. None of these CSP's are yet as good as the commercially available CSP (DNB-(*S*)-Leu-aminopropyl silica and DNB-(*R*)-PG-aminopropyl silica) **(Figure 6)**. Figure 6 also shows the CSP's that were prepared and tested against four analytes.[33] For example, the best separation for analytes B and C was with CSP 12.



Scheme 11– Synthetic Routes For The Preparation Of CSP's.[33]

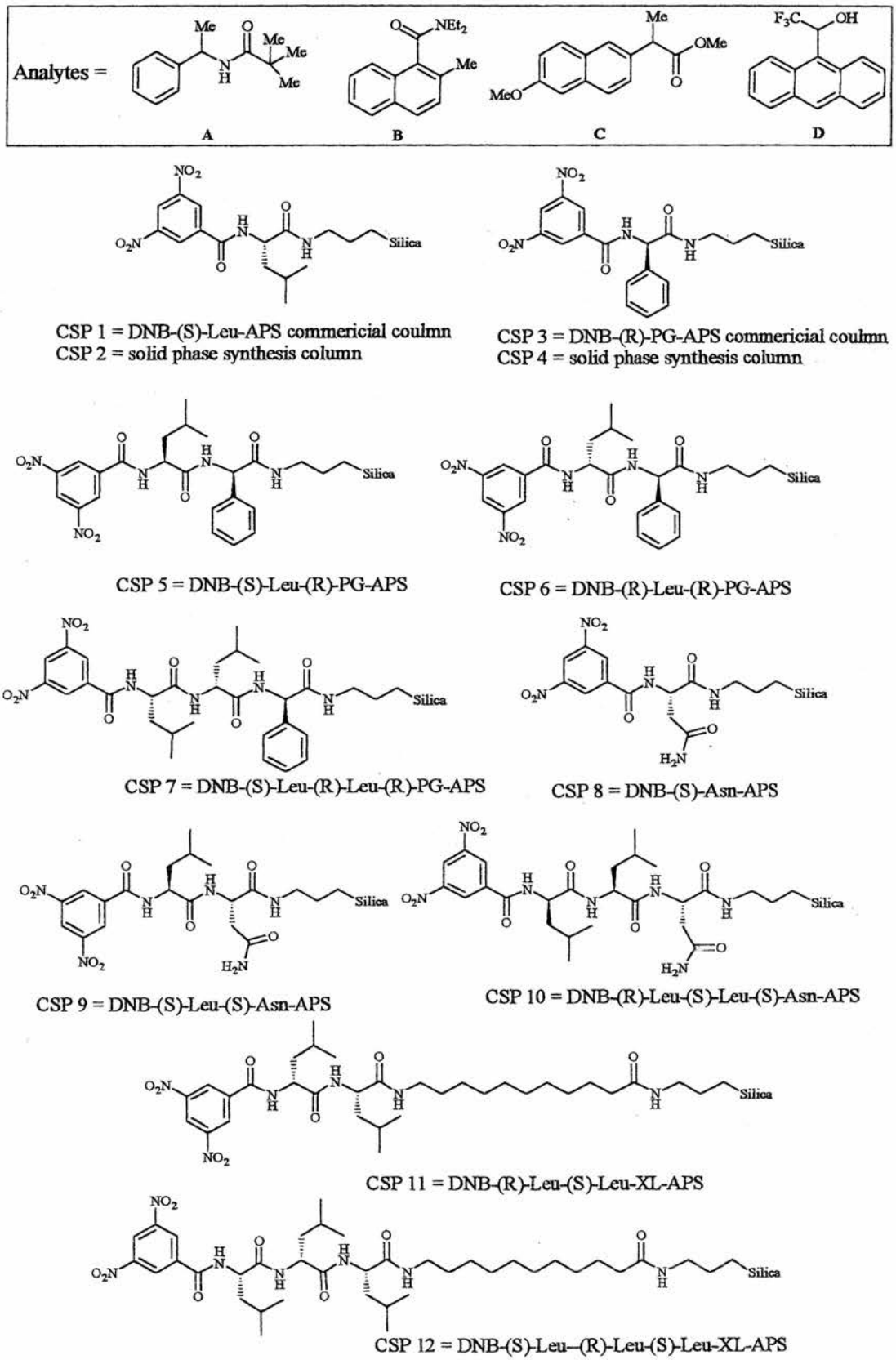


Figure 6 – Analysts used to Test the Ability of New CSP's to Separate a Racemic Mixture.[33]

A large number of CSPs were prepared and screened to gain information on which structures gave good separation. This was achieved effectively by the development of a microscale synthesis and screening protocol.[36] A library of 50 DNB dipeptide CSPs were synthesised on a 50 mg scale using a combination of five different amino acids (valine, glutamine, phenylalanine, phenylglycine and proline) **(Figure 7)**.

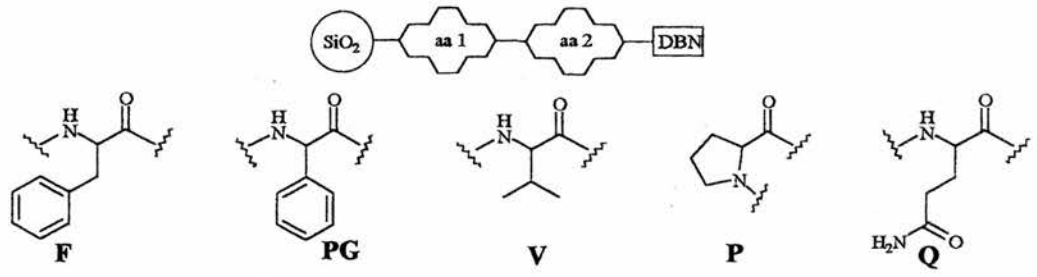


Figure 7 – General Structure of CSP's Combinatorial Library.[36]

A few milligrams of each CSP were then put in an autosampler and a racemic solution of *N*- (2-naphthyl) alanine diethylamide was added to each, then the mixtures were left for 30 mins. The solutions were then analysed by HPLC to see the concentrations of the two enantiomers. The extent of reduction in concentration of one enantiomer in the solution determined how selective the CSP was. Once all the combinations had been tested, a graph of the results was plotted which clearly showed the most promising CSP's **(Figure 8)**. The active CSP's were found to have the following structural features: the first amino acid had the capability to form hydrogen bonds, such as asparagine and aspartic acid; bulky groups such as leucine and valine are required in the second amino acid position.

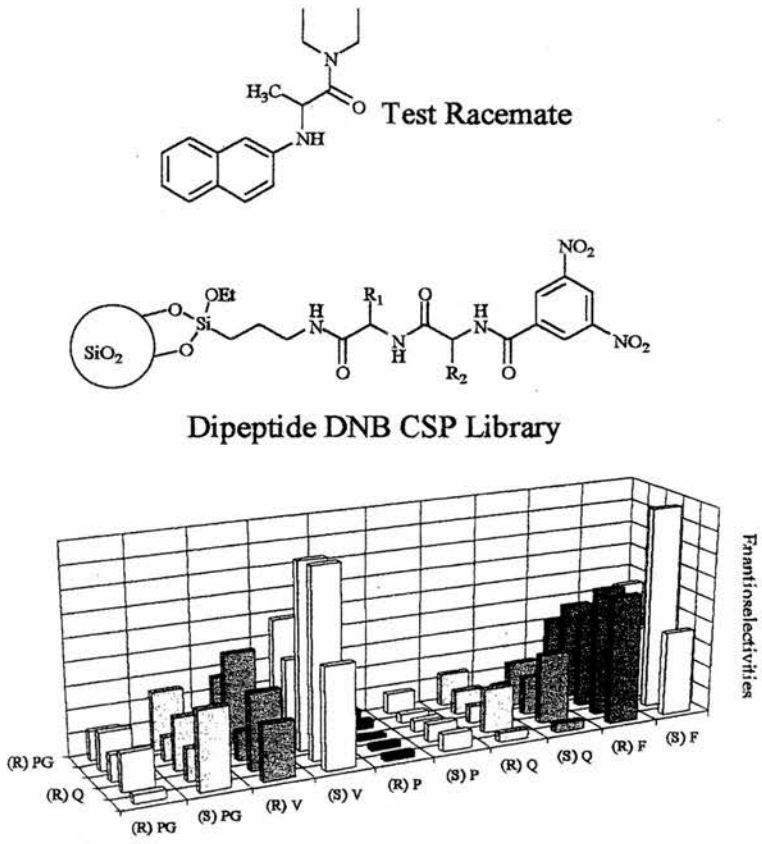


Figure 8 – Results from Screening a Library Of 50 dipeptides CSP's.[36]

In some catalysts and CSPs, C_2 symmetry has been incorporated into the design to enhance selectivity. Pirkle and co-workers[37] have investigated whether C_2 symmetry in the analytes is important to get good enantioselectivity. Various CSPs were studied using the analytes showed in Figure 9. The results show there was no overall benefit from having C_2 symmetry. Where a CSP showed better enantioselectivity for the C_2 analytes, it was because the analyte could interact with two selectors simultaneously.

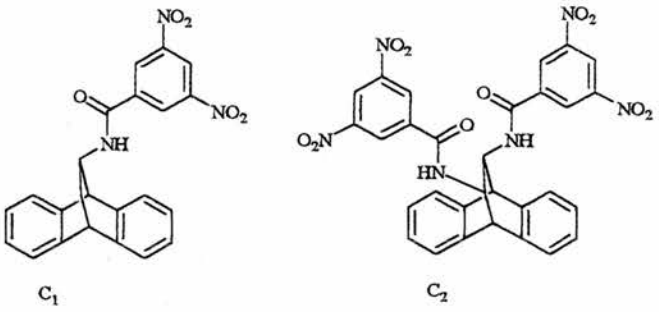
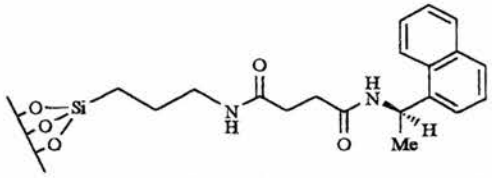


Figure 9 – C_1 and C_2 Analytes Used to Test Whether C_2 Symmetry is Important for Enantioselectivity.[37]

1.6.3 Synthesis of Chiral Stationary Phases Based on MCM-41.

Most chiral stationary phases are based on silica, but MCM-41 has also been used as a support.[38] (*R*)-1-Naphthyl-ethylamine was coupled to aminopropyl functionalised MCM-41 using a spacer molecule of succinic acid **(Figure 10)**. This new CSP was investigated for its ability to resolve racemic dinitrobenzyl derivatives of naphthylethylamine. The CSP based on MCM-41 gave better results compared to the silica-based control. This is because of the difference in surface area and higher coverage of chiral selector. The MCM-41 CSP shows promising results, but further investigation is needed.



MCM-41 functionalised with (R)-napthylethylamine

Test Racemates

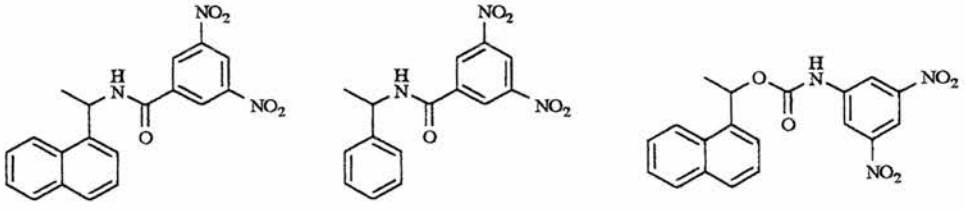


Figure 10 – Chiral HPLC Stationary Phase Based On MCM-41.[38]

1.7 Aims and Objectives of the Current Work.

This thesis reports:-

- Preparation and characterisation of aminopropyl MCM-41 (Chapter 2).
- Further modification of aminopropyl MCM-41 (and aminopropyl silica with amino acids (Chapter 2)
- Preparation of MCM-41 and silica supported oxazaborolidines (Chapter 2).
- Testing MCM-41 supported amino acids as potential catalysts for the asymmetric epoxidation of chalcone (Chapter 3).
- Testing Silica supported amino acids as potential catalysts for the asymmetric cyclisation of epoxy alcohols (Chapter 4).
- Testing MCM-41 and silica supported oxazaborolidines as potential catalysts for the asymmetric reduction of imines and ketones (Chapter 5).

1.8 References

1 J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt, C. T-W. Chu, D. H. Olson, E. W. Sheppard, S. B. McCullen, J. B. Higgins and J. L. Schlenker, *J. Am. Chem. Soc.*, 1992, **114**, 10834.

2 C. E. Fowler, B. Lebeau and S. Mann, *Chem. Commun.*, 1998, 1825.

3 A. Serilevy, S. West and W. G. Richards, *J. Med. Chem.*, 1994, **37**, 1727.

4 A. J. Hutt and J. O'Grady, *J. Antimicrob. Chemother.*, 1996, **37**, 7.

5 H. J. Federsel, *Endeavour*, 1994, **18**, 164.

6 Q. H. Yang, M. J. Khoury, L. M. James, R. S. Olney, L. J. Paulozzi and J. D. Erickson, *Am. J. Med. Gen.*, 1997, **73**, 251.

7 J. Strube, S. Haumreisser, H. SchmidtTraub, M. Schulte and R. Ditz, *Org. Proc. Res. Dev.*, 1998, **2**, 305.

8 A. Serilevy and W. G. Richards, *Tetrahedron: Asymmetry*, 1993, **4**, 1917.

9 S. R. Perrin and W. H. Pirkle, *ACS Symposium Series*, 1991, **471**, 43.

10 Studies in Surface Science and Catalysis, Elsevier Science, 1995, Vol. 93, p. 149.

11 D. Brunel, A. Cauvel, F. Fajula and F. DiRenzo, *Stud. Surf. Sci. Cat.*, 1995, **97**, 173.

12 A. Sinha-Bagchi, C. S. Sinha and E. Keinin, *Tetrahedron: Asymmetry*, 1995, **6**, 2889.

13 J. Y. Ying, C. P. Mehnert and M. S. Wong, *Angew. Chem., Int. Ed.*, 1999, **38**, 56.

14 M. T. J. Keene, R. Denoyel and P. L. Llewellyn, *Chem. Commun.*, 1998, 2203.

15 D. Das and C-M. Tsai, S. F. Cheng, *Chem. Commun.*, 1999, 473.

16 J. H. Clarke and D. J. Macquarrie, *Chem. Commun.*, 1998, 853.

17 J. P. Bezombes, C. Chuit, R. J. P. Corriu and C. Reyé, *J. Mater. Chem.*, 1998, **8**, 1749.

18 J. Aguado, D. P. Serrano, M. D. Romero and J. M. Escola, *Chem. Commun.*, 1996, 725.

19 R. R. Rao, B. M. Weckhuysen and R. A. Schoonheydt, *Chem. Commun.*, 1999, 445.

20 T. Mashmeyer, F. Rey, G. Sankar and J. M. Thomas, *Nature*, 1995, **378**, 159.

21 R. Clarke, M. Gahagan, R. K. Mackie, D. F. Foster, D. J. Cole-Hamilton, M. Nicol and A. W. Montford, *J. Chem. Soc., Dalton Trans.*, 1995, 1221.

22 M. Laspéras, T. Llorett, L. Chaves, I. Rodriguez, A. Cauvel and D. Brunel, *Stud. Surf. Sci. Cat.*, 1997, **108**, 75.

23 N. Bellocq, D. Burnel, M. Laspéras and P. Moreau, *Stud. Surf. Sci. Cat.*, 1997, **109**, 485.

24 M. Laspéras, N. Bellocq, D. Burnel and P. Moreau, *Tetrahedron: Asymmetry*, 1998, **9**, 3035.

25 B. F. G. Johnson, S. A. Raynor, D. S. Shephard, T. Mashmeyer, J. M. Thomas, G. Sankar, S. Bromley, R. Oldroyd, L. Glaggen and M. D. Mantle, *Chem. Commun.*, 1999, 1167.

26 E. J. Corley, A. Guzman-Perez and M. C. Noe, *J. Am. Chem. Soc.*, 1995, **117**, 10805.

27 F. J. A. D. Bakkeren, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, 1996, **52**, 7901.

28 P. O. Norrby and K. P. Gable, *J. Chem. Soc., Perkin Trans. 2*, 1996, 171.

29 B. B. Lohray, E. Nandanan and V. Bhushan, *Tetrahedron: Asymmetry*, 1996, **7**, 2805.

30 C. Bolm and A. Gerlach, *Eur. J. Org. Chem.*, 1998, 21.

31 F. Hunter, Honours Thesis, University of St Andrews, 1998.

32 R. J. Clark and I. J. Shannon, *Chem. Commun.*, 2001, 1936.

33 C. J. Welch, G. Bhat and M. N. Protopopova, *Enantiomer*, 1998, **3**, 463.

34 E. J. Kitka and E. Grushka, *J. Chromatogr.*, 1977, **135**, 367.

35 W. A. Howard, T. B. Hsu and L. B. Rogers and D. A. Nelson, *Anal. Chem.*, 1985, **57**, 606.

36 C. J. Welch, M. N. Protopopova and G. Bhat, *Enantiomer*, 1998, **3**, 471.

37 W. H. Pirkle, Y. L. Liu and C. J. Welch, *Enantiomer*, 1998, **3**, 477.

38 C. Thoelen, K. Van de Walle, I. F. J. Vankelecom and P. A. Jacobs, *Chem. Commun.*, 1999, 1841.

Chapter 2

Preparation and Modification of MCM-41.

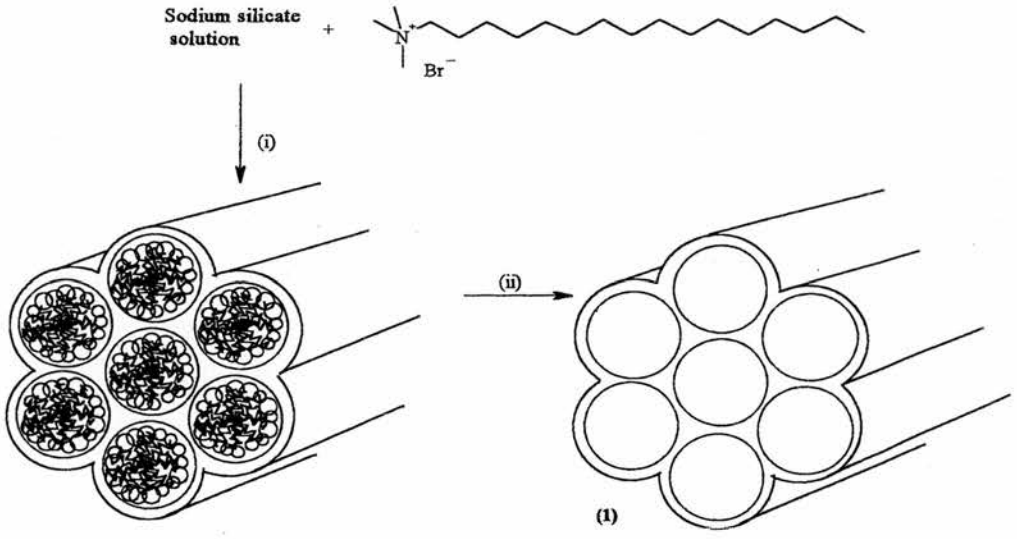
2.1 Results and Discussion

2.1.1 Synthesis of MCM-41.

There are many different methods for synthesising MCM-41. The method used depends on the source of the reagents; even the quality of distilled water can affect the reaction. The MCM-41 used in this project was synthesised at the University of St Andrews, where a hydrothermal synthesis method had already been found to work in those laboratories, using sodium silicate solution from Aldrich and the distilled water available in house. However, the source of the surfactant caused some problems.[1,2] It has been found that the cetyltrimethylammonium bromide (CTAB) from Aldrich will produce MCM-41 but if obtained from Lancaster then the synthesis did not work. As the MCM-41 process is reliant on the formation of micelles, all the factors that affect micelle formation also affect this process such as pH, stirring rate and temperature.

MCM-41 was successfully prepared repeatedly, by first mixing sodium silicate solution, CTAB, water and concentrated sulfuric acid together. This resultant mixture was stirred for 45 minutes, transferred to high density polypropylene bottles and heated in an oven at 98 °C for 6 days. This part of the preparation had to be carried out in plastic apparatus. If glassware is used the impurities in the glass, such as borates, can contaminate the MCM-41. Once the MCM-41 has formed then it can be used in glassware. Therefore, after the MCM-41 had been taken out of the oven the rest of the preparation and subsequent reactions could be carried out in glassware. The MCM-41 in the hydrothermal synthesis mixture was filtered to remove most of the surfactant until the filtrate was pH 8 or lower. The pH is an indication of the amount of surfactant still present in the MCM-41 and if the pH of the filtrate is greater than 8, then there is too much surfactant still left in the MCM-41 to calcine. If

this is the case when the MCM-41 is calcined there is a risk of an explosion and/ or fire when the compound is calcined under oxygen. An XRD of the product was taken at this time to check that the desired reaction had occurred, that MCM-41 had been formed and not amphorous silica **(Figure 11)**. The next step was to calcine the solid to burn off the remaining surfactant and to produce MCM-41. Another XRD was then taken to make sure that the pores had not collapsed during the removal of the surfactant by calcining **(Scheme 11 and Figure 12)**. Using this method 18.7 g of sodium silicate solution (density = 1.390) gave 1.89 g of MCM-41 **(1)**.



Reagents and conditions: - (i) 98 °C, 6 days, (ii) 550 °C, 1 hr, N_2 then 6 hrs, O_2

Scheme 12 – MCM-41 (1) Synthesis.[1,2]

Powder X-ray diffraction gives a fingerprint for the sample and therefore can be used to determine whether MCM-41 has been formed. In this case, the spectrum shows the short range order of hexagonal array of pores. There is a small amount of long range order in the silica walls but this is very small as essentially the walls are amorphous silica **(Table 2, Figures 11 and 12)**. The XRD also shows that there is some contraction in the pore diameter as the peak originally at 2.2 ° shifts slightly after calcination to 2.5 °. This equates with a contraction of the pore diameter from 40.1 Å

to a pore diameter of 36.1 Å after calcination. Bragg's law ($n\lambda=2d\sin\theta$) converts the 2 θ values (obtained in the XRD) to the d spacings which in this case gives the pore diameters. (e.g. 2 θ = 2.2 therefore $d = \lambda/(2\sin\theta) = 1.54/(2x\sin(1.1) = 40.1$ Å) **(Table 2)** (See Appendix 6.1).

	Before Calcination				**After Calcination**			
Miller plane	100	110	200	210	100	110	200	210
2 θ/ °	2.2	3.8	4.3	5.7	2.5	4.2	4.8	6.2
d spacing/ Å[a]	40.1	23.6	20.3	15.5	36.1	21.0	18.4	14.4

[a] d spacing gives the pore diameter, this is calculated using Bragg's law (Wavelength XRD acquired at λ = K Alpha = 0.154 nm)

Table 2 – D-Spacing for MCM-41 (1).

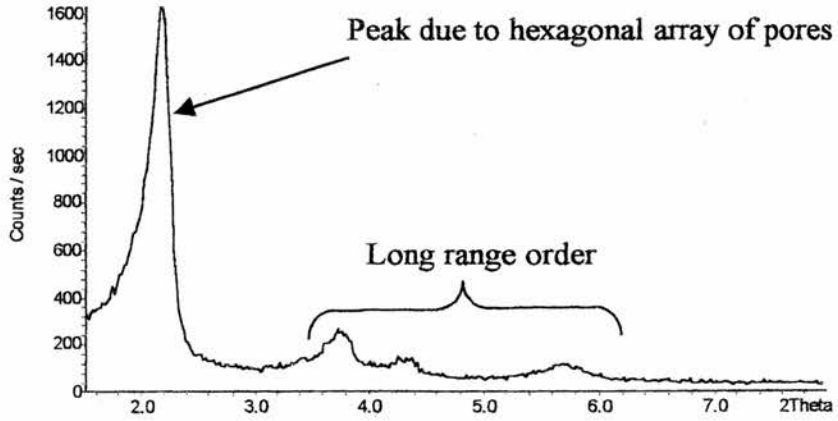


Figure 11 – XRD of MCM-41 (1) before Calcination.

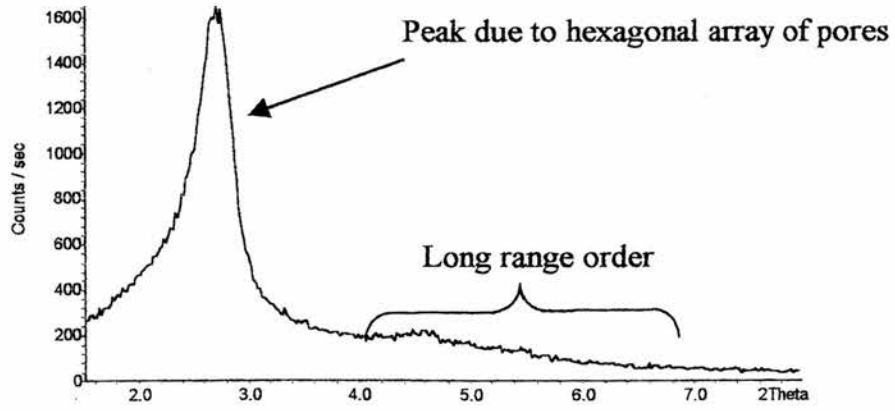


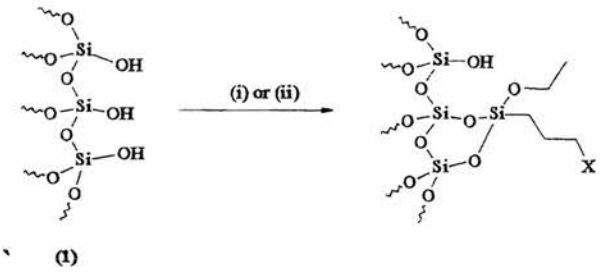
Figure 12 – XRD of MCM-41 (1) after Calcination.

2.1.2. Functionalisation of MCM-41 (1).

2.1.2.1 Preparation of Aminopropyl MCM-41 (2).

MCM-41 **(1)** must be pre-activated before it can be functionalised. This was achieved by removal of all the co-ordinated water by heating to 160 °C under high vacuum. After the co-ordinated water has been removed the silane reagent (3-aminopropyl) triethoxysilane can be added and this will react with the silanols on the surface of the pore.[2] In the functionalised MCM-41 it is not clear if all the ethoxy groups have reacted, or whether the silane has only reacted displacing two ethoxy groups as ethanol and leaving a single ethoxy group on the silicon. **Scheme 12** shows the situation where two ethoxy groups have been eliminated. Comparing the loading calculated from the nitrogen elemental analysis and carbon elemental analysis it appears than on average 2.5 ethoxy groups have been displaced. This is determined by calculating the loading from the nitrogen elemental analysis and then calculating the number of carbons per nitrogen. In this case, the ratio of nitrogen to carbon comes out as 1:4. The propyl group accounts for three of the carbons so there is one out of a possible six carbons from the ethoxy groups. Therefore on average half an ethoxy group remains, or 2.5 ethoxy groups have been displaced. Solid state NMR also indicates the presence of ethoxy groups (Section 2.1.2.2.3).

A similar procedure was tried to tether on a 3-chloropropyl linker. However, when the elemental analysis of the resulting material was obtained there was nitrogen present. This must be due to the triethylamine which is present in the reaction. It is unclear wither the triethylamine is co-ordinating strongly or has reacted with the 3-chloropropyl linker but it could not be washed off the material. Therefore, synthesis was successfully achieved by using DIEA instead of triethylamine as the base. The elemental analysis of this material did not contain any nitrogen **(Scheme 12)**.



Average 0.5 ethoxy group per aminopropyl group.
X = NH_2 **(2)** Loading = 1.8 mmol g^{-1}
X = Cl **(3)** Loading = 1.8 mmol g^{-1}

Reagents and conditions: - (i) X = NH_2 $(EtO)_3Si(CH_2)_3NH_2$, Et_2O, Et_3N, 40°C, 3 hr; or (ii) X = Cl $(EtO)_3Si(CH_2)_3Cl$, Et_2O, DIEA, 40°C, 3 hr.

Scheme 12 – Modification of MCM-41 (1) or Silica Gel.[2]

It is possible to deactivate the external surface of MCM-41 **(1)** by 'capping' with dichlorodimethylsilane.[2] This makes calculating the loading of the linker by elemental analysis less accurate. If the solid is not 'capped' then the elemental analysis is for one reaction and the extent of that reaction (or loading) can be calculated. If the solid is 'capped' then the elemental analysis gives a loading which is the average of the loading of the 'capping' reaction and the silane reaction. Although the amount of reagents used in the 'capping' reaction are much less than that for the silane reaction it will have an affect on the calculated loading. As the solids being investigated are mesoporous, most of the surface is on the inside of the pores. A approximate calculation suggests that if the particle diameter is 2 μm then the percentage of the surface which is external is 0.03 %. This is the smallest that the particle size can be, because the MCM-41 does not pass through the sinter funnel used (grade 3). Increasing the size of the particle reduces this percentage further (Appendix 6.3). When looking in the first instance for activity in either catalysis or chiral recognition, the small amount of linker that might react on the surface will not be significant. For this reason, and to simplify derivatisation protocols, we chose to work with 'uncapped' aminopropyl MCM-41 in the first instance. This will also make the comparison with aminopropyl functionalised silica more accurate. Once the

organic moieties that give activity are determined then we could go back and optimise the system and see the effect of capping the external surface, as well as the effect of loading. To try to aid our understanding of what was possible in characterisation of these materials, acetamidopropyl functionalised MCM-41 **(4)** was prepared. This was a simple compound which contained an amide bond which all subsequent compounds would contain and allowed us to assign peaks in spectra (section 2.1.2.2.3)

2.1.2.2 Modification of 3-Aminopropyl functionalised MCM-41 (2) with Amino Acids.

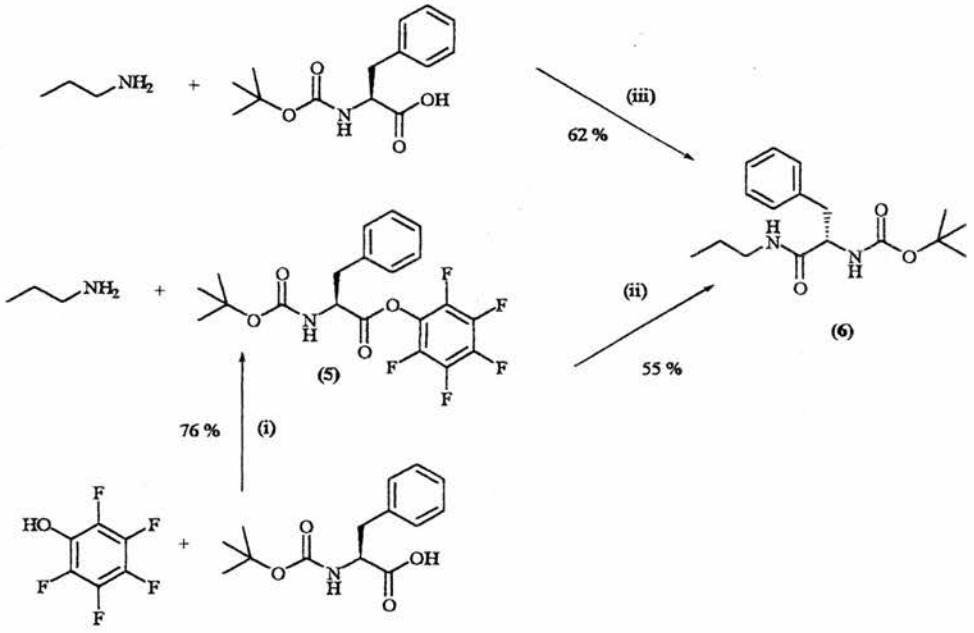
Methodologies for asymmetric synthesis involve subjecting the reactants to a chiral environment. This is where chiral cavities could become useful, because as the reactants pass through the chiral cavity/pore they can interact with the chiral environment.

2.1.2.2.1 Model Studies for Amino Acid Couplings onto 3-Aminopropyl functionalised MCM-41 **(2)**.

To prepare chiral cavities with MCM-41 **(1)** a chiral acid was attached to the surface of the pore via the aminopropyl-linker **(2)**, forming an amide linkage. As it is difficult to know exactly what is happening during the reaction with aminopropyl MCM-41, propylamine was first used as a solution model.

Various coupling procedures were investigated using the model system; these were DCC, PyBOP and Pfp ester. DCC is not suitable to couple onto aminopropyl functionalised MCM-41 as the by-product from the reaction is urea, which would contaminate the product. EDCl is an analogue of DCC, which forms a water soluble

urea by-product. This would also be a disadvantage because as we are working with molecular sieves they co-ordinate water and protic solvents very tightly and it would be difficult to remove these without destroying the organic group tethered to the support. Therefore, PyBOP and Pfp ester methods were compared **(Scheme 13)**. In fact, the Pfp ester method actually uses DCC to prepare the Pfp ester in the first place. It was found that the PyBOP method gave the best overall yields and it will be shown that it was also the best method when aminopropyl functionalised MCM-41 was the substrate.



Reagents and conditions: - (i) DCC, dioxane / DMF (4:1), 0 °C to RT, 2 hr; (ii) Acetone, $NaHCO_3$, 24 hrs. (iii) PyBOP, DIEA, acetonitrile RT, 2 hrs;

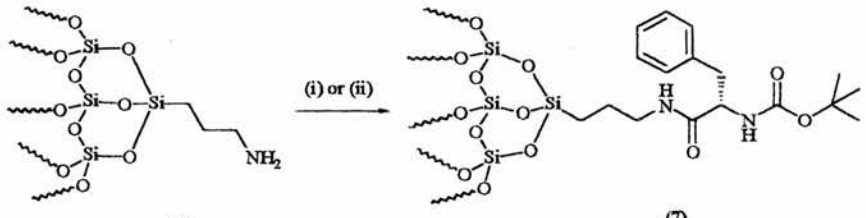
Scheme 13 – Solution Couplings of Propylamine and Boc-L-Phenylalanine.[3,4]

Other coupling procedures were also investigated using Mosher's acid. We were interested in Mosher's acid as it cannot racemise, unlike amino acids. As well as the methods mentioned above the mixed anhydride method and preparation of the acid chloride with subsequent coupling were examined. Apart from preparation of the

acid chloride and subsequent coupling, which is not compatible with amino acids, PyBOP proved again to give the best results.

2.1.2.2.2 Peptide Coupling onto Aminopropyl Silicates

The results from the solution model studies were applied to the coupling of Boc-L-phenylalanine to aminopropyl-functionalised MCM-41 **(2) (Scheme 14)**. Both the Pfp ester and PyBOP methods were tried.[3,4] From the elemental analysis it appears that both reactions have occurred to approximately the same extent. Overall, PyBOP gave the better results because the procedure is one step instead of the two for the Pfp ester method. Another consideration is that the PyBOP reaction is also faster, taking approximately 2 hours instead of 24 hours for the Pfp esters **(Scheme 13)**.



(2) (7)

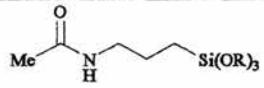
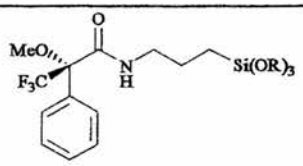
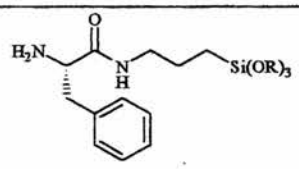
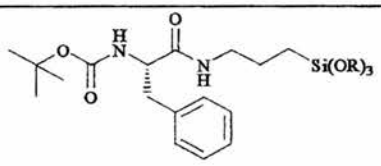
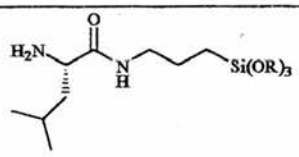
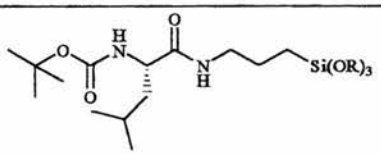
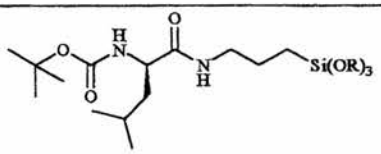
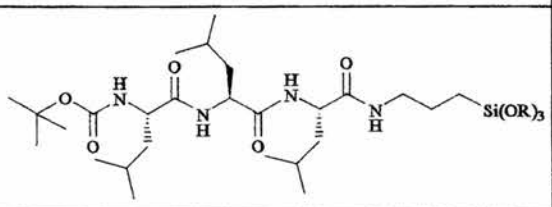
Pfp Method: Loading = 1.2 mmol g^{-1}
PyBOP Method: Loading = 1.3 mmol g^{-1}

Reagents and conditions: - (i) Boc-L-Phenylalanine, PyBOP, DIEA, acetonitrile RT., 2 hrs; or (ii) Phenylalanine Pfp ester, DIEA, Acetonitrile, RT., 24 hrs.

Scheme 14 – Functionalisation of Aminopropyl functionalised MCM-41 (2) with Boc-L-Phenylalanine.[3,4]

The PyBOP procedure was then used to synthesise a range of inorganic - organic hybrids **(Table 3)**. Amino acids can be used as chiral modifiers but there is always a problem with racemisation due to the acidic α - proton. However, the advantage lies in the fact that they are some of the cheapest chiral reagents available. Generally both enantiomers are readily available and they contain a large amount of functionality in

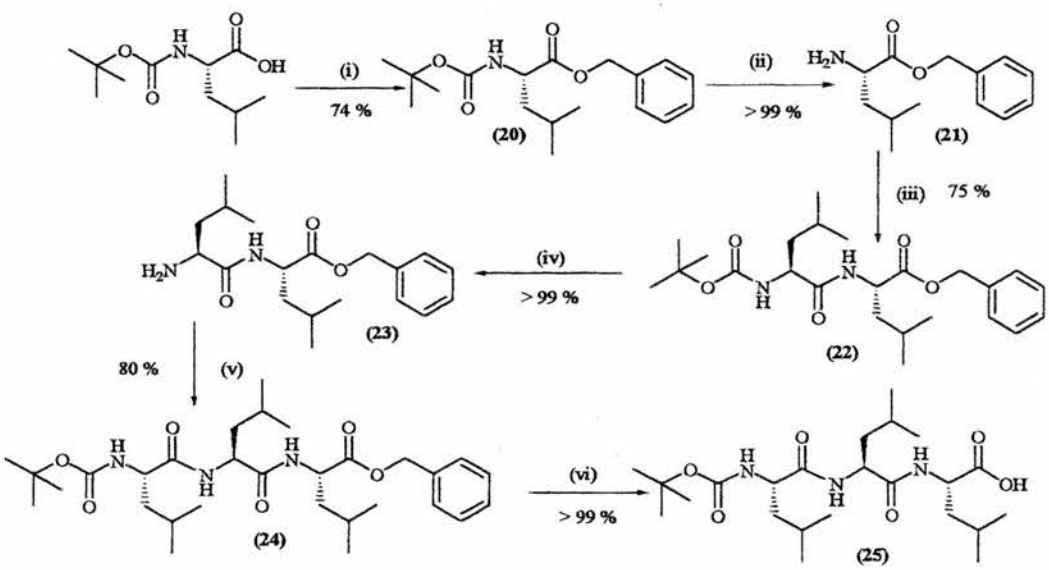
both the side chain and the protecting groups on nitrogen. Mosher's acid was also tethered to aminopropyl MCM-41, since it cannot racemise as there is no acidic proton. As well as the MCM-41 supported compounds, silica-based materials were also prepared in this study. Although aminopropyl functionalised silica **(12)** was prepared the inorganic hybids prepared and tested were actually prepared using commercially available aminopropyl functionalised silica from Fluka. When this material was purchased no information about the loading was available. When we enquired the supplier quoted a loading of 5 mmol g^{-1}. This is far higher than the calculated MCM-41 loading and as MCM-41 has is reported to produce larger loading than silica this quoted loading is unlikely. When elemental analysis was conducted on the Fluka material, the loading came out as 1 mmol g^{-1}, which is more reasonable and agrees with the material that was made herein **(12)**.

Organic group tethered to the silicate[a]	MCM-41 based		Silica Based	
	No.[b]	Loading[c]	No.[b]	Loading[c]
	**2**	1.8	**12**	1.0
	**3**	2.0	-	-
	**4**	1.4	-	-
	**11**	1.7	**17**	0.5
	-	-	**16**	0.9
	**7**	1.2	**15**	1.0
	**8**	0.8	**13**	0.7
	**9**	1.0	**14**	0.9
	**10**	1.0	-	-
	-	-	**26**	0.6

[a] R= silica or MCM-41 surface. [b] Compound number in experimental. [c] in mmol g^{-1}

Table 3 - Inorganic - Organic Hybrids with Amino Acids and Mosher's acid Tethered to MCM-41 (1) and Silica.

Most of the MCM-41 and silica based materials prepared just required one PyBOP coupling of an amino acid to the aminopropyl functionalised silicate. However, the Boc – tri leucinyl amidopropyl functionalised silica **(26)** was slightly different. In this case the trileucine was prepared first in solution and then tethered to the aminopropyl silica. The peptide was first prepared in solution so that it could be fully characterised and this was achieved by PyBOP peptide couplings followed by TFA deprotection **(Scheme 15)**.[4] All the compounds were characterised by NMR, IR, accurate mass spectrometry and optical rotation where appropriate.

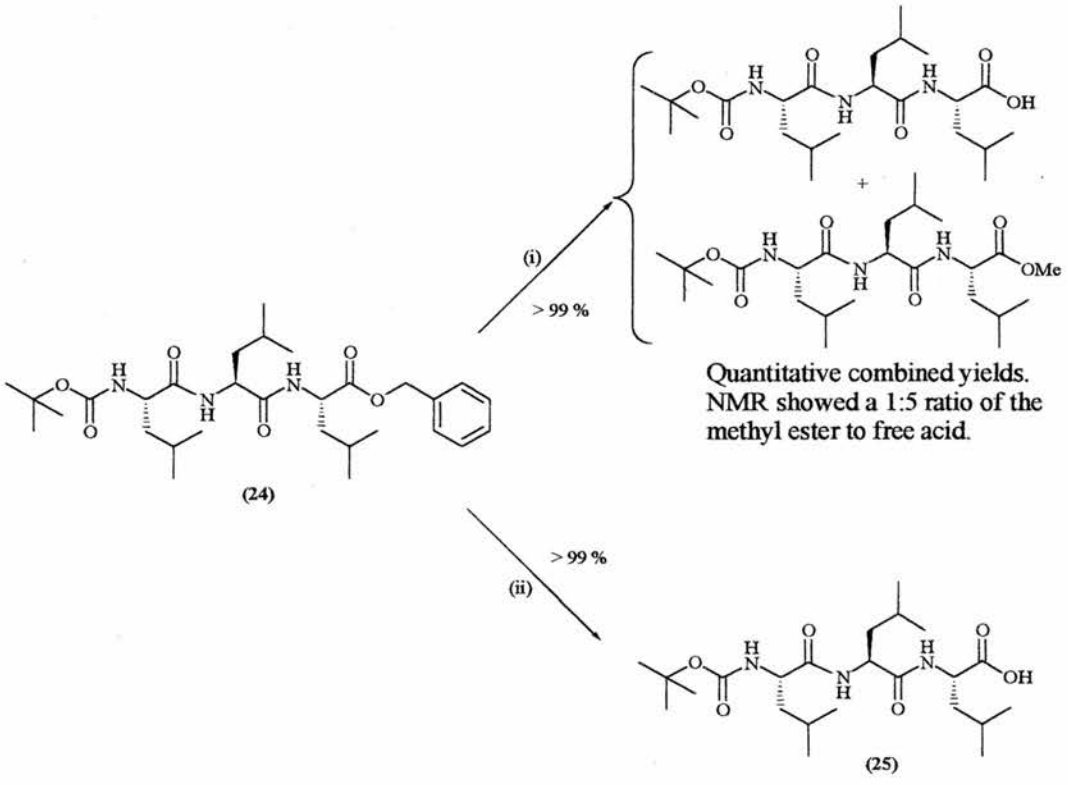


Reagents and conditions: - (i) BnBr, $AgCO_3$, RT, 24 hrs, (ii) TFA/DCM (1:1), 30 min, (iii) Boc-L-leucine, PyBOP, DIEA, acetonitrile RT., 3 hrs, (iv) TFA/DCM (1:1), 30 min, (v) Boc-L-leucine, PyBOP, DIEA, acetonitrile RT., 3 hrs, (vi) H_2, Pd/C, acetic acid, RT., 24 hrs.

Scheme 15 - Synthesis of Boc L Tri Leucine.[4]

The only problem that occurred was during the removal of the benzyl protecting group by hydrogenation. This was first tried in methanol but it was found that approximately 20 % of the product was the methyl ester **(Scheme 16)**. This was either from transesterification of the benzyl ester or esterification of the free acid. It

proved impossible to either separate the two products and obtained the free acid, or deprotect the methyl ester and keep the tripeptide intact. However, the deprotection of the benzyl ester was successfully achieved by using acetic acid rather than methanol as the solvent.



Reagents and conditions: - (i) H_2, Pd/C, methanol, RT., 24 hrs, (ii) H_2, Pd/C, acetic acid, RT., 24 hrs

Scheme 16 - Deprotection of A Benzyl Ester.

Once the tripeptide had been prepared it was coupled to aminopropyl silica by the same procedure as for the other amino acid functionalised silicates.

2.1.2.2.3 Characterisation of Amino Acid Modified MCM-41 and Silica.

The compounds discussed above were characterised by elemental analysis, IR spectroscopy **(Figure 13)** and solid state ^{13}C NMR spectroscopy **(Figure 14)**. These

are the only techniques that can be used to characterise the organic groups that have been tethered to the silicate. Elemental analysis was performed to determine the loadings of the modified silicate as well as the extent of the reaction. As we are working with such low loading, the elemental analysis is not accurate as the errors are so large. This means that the loadings calculated from the elemental analysis can only be taken as an approximation. The other problem with determining loadings by this method is that the calculations only take into account one species tethered onto the support. The likelihood of this is very remote and there is much more likely to be a mixture of surface species. The prime example is the number of ethoxy groups still attached to the silane, which has already been discussed.

The second technique used was IR spectroscopy using KBr discs **(Figure 13)**. The problem here is that some of these materials (especially the silica based compounds) are very hard to convert into KBr discs. This is because the discs need to be thin enough to be transparent for the IR spectrometer. At this thickness, they tend to just fall apart or crack in the press. Nevertheless, once they have been formed they can show whether a reaction has taken place, especially in this case as the coupling step introduced a carbonyl group which is very characteristic in the IR spectrum.

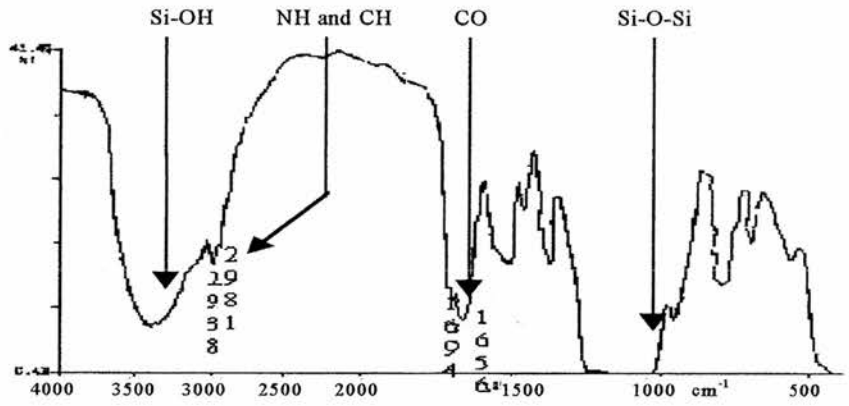


Figure 13 - IR Spectrum of Boc-L-Phenylalaninyl Amidopropyl Functionalised MCM-41

The IR shows the CH (2938 cm^{-1}) and NH (2981 cm^{-1}) stretches as well as the CO stretch (1694 and 1656 cm^{-1}).

The last technique that can be used to characterise inorganic-organic hybids is ^{13}C solid state NMR **(Figure 14)**. However, because of the low loadings, the spectrum in figure 14 took a day to acquire. The other problem is that as the spectrum is very noisy only approximate assignments can be made. As with the IR, the presence of carbonyl groups as well as the aromatic group of phenylalanine can be observed in the NMR spectrum.

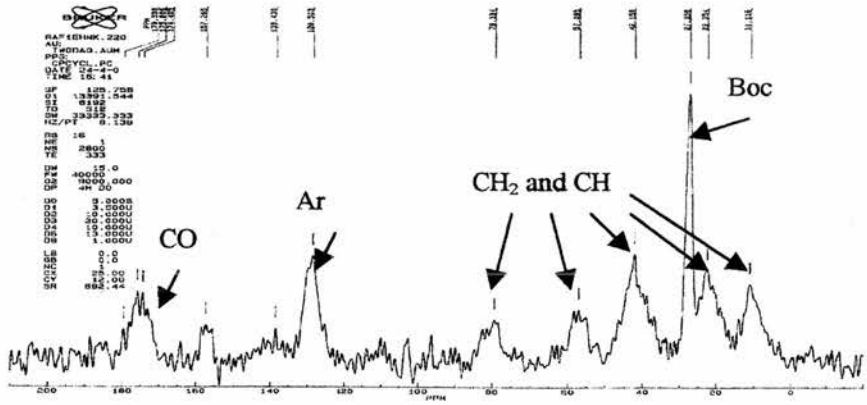


Figure 14 - ^{13}C NMR Spectrum of Boc L Phenylalaninyl Amidopropyl Functionalised Silica

The ^{13}C NMR spectrum shows the CO, phenyl and the propyl group carbon atoms. As part of the peaks labelled CH_2 and CH, there are the ethoxy groups, which have not been eliminated. This is seen because the solid state NMR of aminopropyl MCM-41 has four distinct peaks in the CH_2/ CH_3 region.

With the above chirally modified MCM-41 and silica materials to hand, their effect on asymmetric epoxidation (Chapter 3) and ring closure reactions (Chapter 4) was investigated.

2.1.3 Preparation of Solid Supported Oxazaborolidines.

2.1.3.1 Introduction.

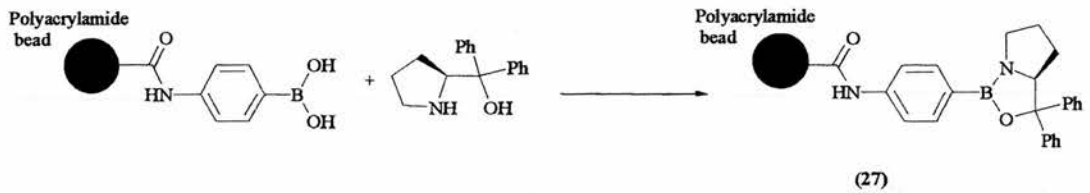
Oxazaborolidines have been used as catalysts for the asymmetric reduction of ketones and more recently for the asymmetric reduction of imines.[5,6] This topic will be discussed in more detail in Chapter 5. As the solution phase reduction of ketones with oxazaborolidine is a useful synthetic procedure, there have been investigations in supporting oxazaborolidines on polymers. This was to enhance the ease of purification and recycling of the oxazaborolidine.

In section 2.1.3.2 the preparation and characterisation of MCM-41 and silica supported oxazaborolidines will be discussed.

2.1.3.2 Preparation Of Polymer Bound Oxazaborolidine. **(27)**

Supporting the oxazaborolidine on the commercially available polyacrylamide supported boronic acid, is the simplest of the proposed supported oxazaborolidines to prepare. (S) α,α Diphenylprolinol was refluxed with the commercially available (Pierce) polyacrylamide supported phenyl boronic acid, with the removal of water by

a Dean-Stark apparatus, to give the supported oxazaborolidine **(Scheme 17)**.[7] The boronic acid loading was100 μl per ml which equated to approximately 100 μl boron in 140 mg resin.



(27)

Reagents and conditions: - (i) Toluene, Dean-Stark, reflux, 18 hrs.

Scheme 17 – Preparation of a Polymer Supported Oxazaborolidine (27).[7]

Although the synthesis was simple, the characterisation was not so straightforward. The extent of the reaction was measured in two ways. Firstly, the weight gain in the polymer and secondly the % C elemental analysis. The yield of the reaction when calculated by weight gain was 98 %. However, when calculated from the elemental analysis, the yield was only 16 %. This illustrates the problem of using elemental analysis for working out loadings. At these types of loading, the percentage increase is so low that, if the error of ± 0.3 % is taken into account, yields of over 100 % can be calculated. The other methods of characterisation that can be performed are IR and solid state NMR but these are not quantitative and the other problem is that the peaks due to the polymer backbone dominate both sets of spectra. The loading from the weight gain was calculated to be 0.55 mmol g^{-1} and this value was used to determine the amount of catalyst to be added to the test reductions (Chapter 5).

The preparation of this supported oxazaborolidine highlights the problems with characterisation once a compound is supported. It is very difficult to know exactly what the species are on the support and the extent of the loading. The techniques that

are used in solution for full characterisation cannot be transferred and used in solid phase chemistry such as ^{1}H NMR, accurate elemental analysis, mass spectrometry and optical rotation for chiral molecules. Therefore, with these techniques available, we can get an indication of the loading but nothing exact.

2.1.3.2 Synthesis of Silicate Supported Oxazaborolidines.

The proposed structure of the silicate supported oxazaborolidines, for testing as potential asymmetric reduction catalysts, are shown in Figure 15.

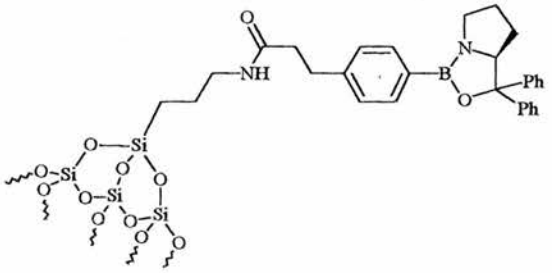
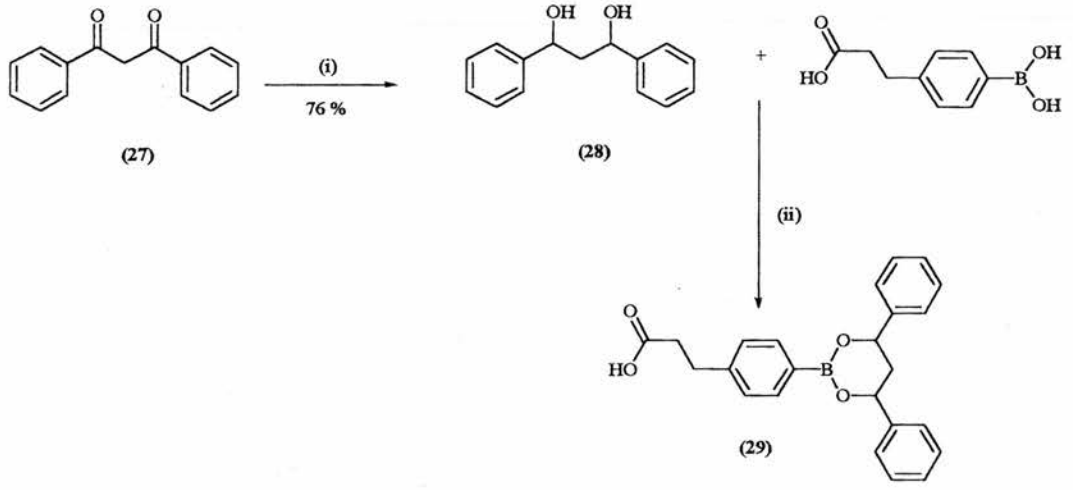


Figure 15 – Proposed Structure of Silicate Supported Oxazaborolidines.

The route used to prepare this catalyst illustrates a way of calculating loading using a protecting group, without relying on elemental analysis. First, the protecting group precursor, 1,3-diphenylpropane-1,3-diol **(28)**, needs to be prepared from commercially available 1,3-dibenzoyl propane, by a simple sodium borohydride reduction **(Scheme 18)**. The diol **(28)** was used for the boron protection because it has a high molecular weight. Therefore, when the protecting group is cleaved the weight of the resulting diol **(28)** will be large enough to weigh accurately. It also produces a UV-fluorescent spot on TLC, so that the reaction can be followed simply. The use of this diol **(28)** for protecting a boronic acid followed by subsequent tethering to a support was developed in house at GSK.

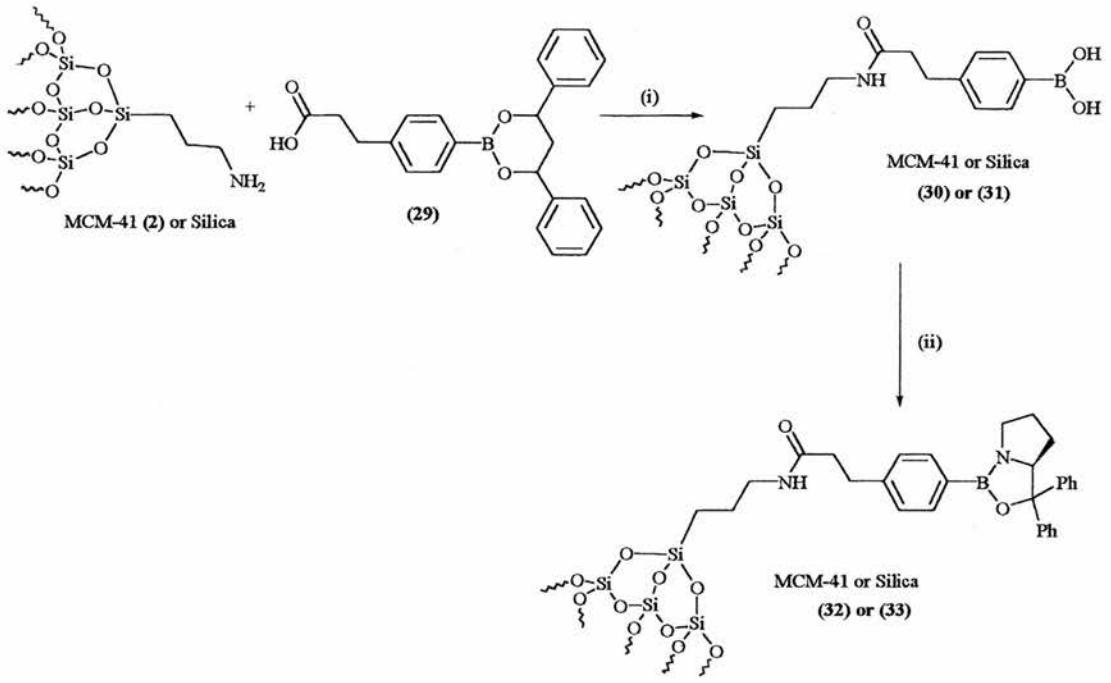
4-(2-Carboxyethyl)benzeneboronic acid is insoluble in normal organic solvents. Therefore, the boronic acid was dissolved in DMF and refluxed with the diol **(28)** in the presence of molecular sieves to give the protected boronic acid **(29)** **(Scheme 18)**.



Reagents and conditions: - (i) $NaBH_4$, ethanol, 3 hrs; (ii) Dean-Stark, toluene, 18 hrs, reflux.

Scheme 18 – Protection of a Boronic Acid.

Boronic acids and their derivatives can be hard to purify and compound **(29)** was no exception. When an NMR of the product **(29)** was taken there were some minor by-products. It proved impossible to recrystallise the product as it only partially solidified and column chromatography did not remove these impurities. This was not a major issue here, as the next step was to react the boronic acid derivative with the aminopropyl functionalised MCM-41 **(2)** or silica (Fluka). Any by-products or solvents could then just be washed off. Accordingly, the crude product was taken on and reacted with the aminopropyl functionalised MCM-41 **(2)** or silica (Fluka) **(Scheme 19)**.



Reagents and conditions: - (i) PyBOP, DIEA, acetonitrile, RT, 18 hrs; (ii) 1 N HCl / THF (1:3), 4 hrs; (ii) Toluene, (S)-α,α-diphenylprolinol, Dean-Stark, reflux, 48 hrs.

Scheme 19 – Preparation of MCM-41 and Silica Supported Oxazaborolidines (32) and (33).[7]

The supported oxazaborolidine could then be prepared in a similar manner to the catalyst in section 2.1.3.1. The solid supported boronic acids **(30 and 31)** were refluxed in a Dean-Stark apparatus with (S)-α,α-diphenylprolinol. This yielded materials **(32)** and **(33)** with a loadings of 0.77 mmol g^{-1} and 0.40 mmol g^{-1}, respectively.

Table 4 shows the intermediates and the final supported oxazaborolidines with their loadings.

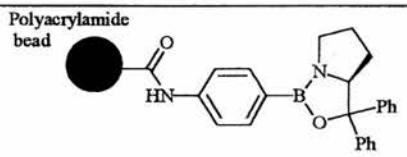
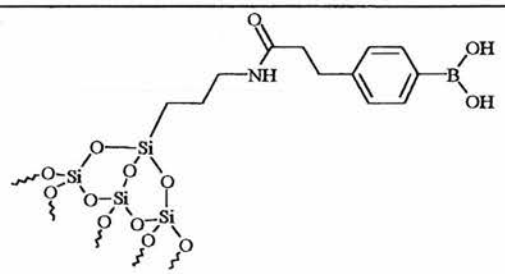
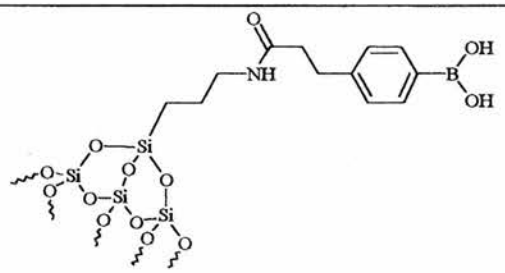
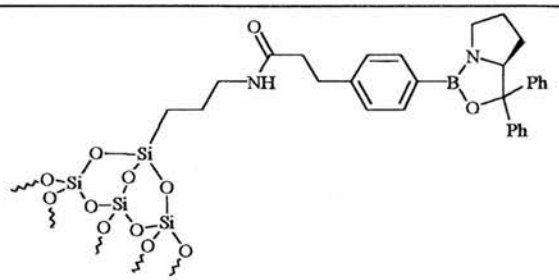
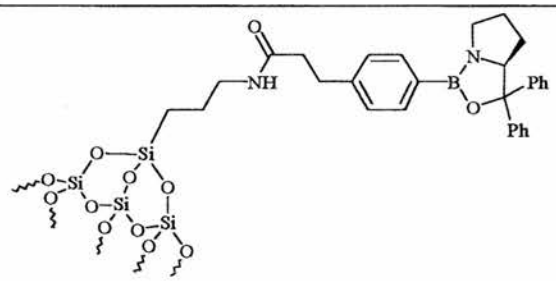
Compounds	Compound No.	Loadings (mmol g^{-1})
	**27**	0.55
 MCM-41	**30**	1.27
 Silica	**31**	0.64
 MCM-41	**32**	0.77
 Silica	**33**	0.40

Table 4 – Loadings of Supported Oxazaborolidines that have been Prepared.

With supported oxazaborolidines shown in table 4 in hand we set about investigating their efficiency as catalysts for asymmetric reduction of ketones and imines (Chapter 5).

2.2 Experimental

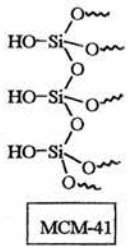
Commercial reagents were used without further purification. All reagents and solvents were dried before use according to standard methods.[8] Toluene, DCM and acetonitrile were dried over calcium hydride. THF and ether were dried over sodium/ benzophenone and methanol was dried over magnesium. Analytical TLC was performed on 0.25 mm precoated silica plates (Whatman, PE SIL G/UV, glass backing) with detection by fluorescence and/or charring and/or iodine and/or ninhydrin dip (0.25 % in acetone) and/or polymolybdic acid dip (5 % in Ethanol) and/or cerium sulphate/ ammonium molybdate tetrahydrate dip [In water (942 ml) cerium sulphate dihydrate (10 g) and ammonium molybdate tetrahydrate (15 g) were added and then conc. H_2SO_4 (58 ml) was added slowly]. Column chromatography was performed on silica gel 60, 35-70 μm (Fluka). Melting points were measured on a Gallenkamp melting point apparatus, and are uncorrected. Optical rotations were measured at the sodium D-line and at ambient temperature with an Optical Activity AA - 10000 polarimeter or with a Perkin Elmer 141 Polarimeter. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. ^1H, ^{19}F and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 spectrometer at 300 MHz, 282 MHz and 75 MHz respectively. ^1H NMR spectra are referenced to $CHCl_3$ (δ_H 7.26 in $CDCl_3$), ^{19}F NMR spectrum were referenced to $CClF_3$ (internal reference) which was set at δ_F 0 and ^{13}C NMR spectrum are referenced to $CDCl_3$ (δ_C 76.9). Solid state NMR was carried out on a Bruker MSL 300 spectrometer with a spinning sample. Powder X-ray diffraction patterns were recorded on a Philips PW 3710 mpd controlled Diffractometer using a Cu K_α source (λ=1.5418Å). Elemental analysis was performed on a Carlo-Erba Instrument Azione model 1106 CHN analyser. IR spectroscopy was carried out on a

Perkin-Elmer 1710 FT-IR spectrometer. MALDI-TOF mass spectrometry was performed on a Micromass TOF Spec 2E spectrometer.

In the following experimental, the elemental analyses of the inorganic-organic hybids have been included as well as the calculated values. These do not agree and the observed values are generally lower than the calculated values. The observed elemental analyses have been included as they prove that organic material has been incorporated onto the silicates. The discrepancy between the observed and calculated elemental analysis has already been discussed in section 2.1.2.2.3.

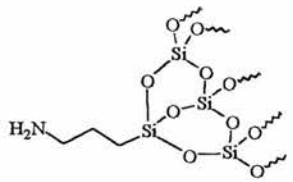
2.2.1 Inorganic - Organic Hybrids Based on MCM-41.

MCM-41 **(1)**



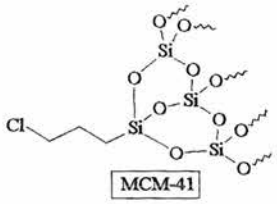
MCM-41 **(1)** was prepared as described by Beck and co-workers.[1] Concentrated sulphuric acid (1.2 g) was added to a stirred solution of sodium silicate (18.7 g, d=1.390 g cm^{-3}) in water (40 ml). After 15 minutes cetyltrimethylammonium bromide (16.77 g) in water (50.5 ml) was added and the mixture was stirred for a further 45 minutes at room temperature. Water (20 ml) was added and the mixture was stirred for a further 10 minutes and then placed in a high-density polypropylene bottle and placed in an oven for six days at 98 °C. The product was filtered and washed with water until the pH of the filtrate was approximately 8 and the white solid was left to dry overnight. The XRD was recorded before calcination. The white solid was placed in a tube furnace, heated to 550 °C at a rate of 10°C min^{-1} under a nitrogen atmosphere, and held there for one hour and then a further six hours under oxygen atmosphere. The sample was cooled at a rate of 20 °C min^{-1} under an oxygen atmosphere to room temperature to give the *title compound* **(1)** as white powder (1.89 g). This procedure was repeated successfully many times with similar yields; ν_{max} (KBr disc) 3414 (OH), 1624 (H_2O), 1029 (Si-O-Si), 796 (Si-O-Si), Found C, 0.18; H, 0.28; N, 0.00 %, (Calc. C, 0.00, N, 0.00 % – H % cannot be calculated as the number of silanols is unknown.).

Aminopropyl- functionalised MCM-41 **(2)**



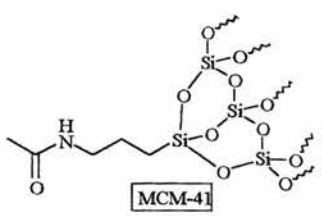
The title compound **(2)** was prepared using the procedure described by Hunter.[2] MCM-41 **(1)** (0.65 g) was heated for one hour to 160 °C under vacuum. Once the flask was cool, it was saturated with a nitrogen atmosphere. Diethyl ether (10 ml) was added to form a suspension. The flask was cooled using isopropanol / dry ice mix and (aminopropyl) triethoxysilane (0.38 ml, 2.235 mmol) was added and the mixture was allowed to return to room temperature. The flask was heated to 40 °C and the product was stirred for one hour. Triethylamine (0.33 ml) in diethyl ether (5 ml) was added and the mixture was stirred for a further two hours at 40 °C. The solid was filtered through a glass sinter and washed with diethyl ether to give the *title compound* **(2)** as a white powder. (0.80 g, 54 % from N elemental analysis, calculated from amount of silane used); ν_{max} (KBr disc) 3423 (NH), 2980 (CH_3), 2932 (CH_2), 1638 (H_2O), 1076 (Si-O-Si), 955 (Si-O-Si), 796 (Si-O-Si), (Lit.[2] 3441 (NH and CH_2), 1633 (H_2O), 1072 (Si-O-Si), 796 (Si-O-Si)); Found; C, 8.60; H, 1.98; N, 2.58 %. (Calc. C, 16.50; H, 2.92; N, 4.81 %; Calculated from the amount of silane initially added and assuming an average of 2.5 ethoxy groups have eliminated - See Appendix 6.2). Loading = 1.8 ± 0.2 mmol g^{-1}.

Chloropropyl- functionalised MCM-41 **(3)**



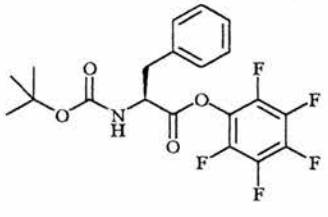
MCM-41 **(1)** (0.65 g) was heated for one hour to 160 °C under vacuum. Once the flask was cool it was saturated with an argon or nitrogen atmosphere and left overnight. Diethyl ether (10 ml) was added to form a suspension and dichlorodimethylsilane (0.011 ml, 0.091 mmol) was added and the suspension was stirred for one hour. The flask was cooled using isopropanol / dry ice mix and (chloropropyl) triethoxysilane (0.54 ml, 2.235 mmol) was added and the mixture was allowed to return to room temperature. The flask was heated to 40 °C and the product stirred for one hour. DIEA (0.41 ml, 2.27 mmol) in diethyl ether (5 ml) was added and the mixture stirred for a further two hours at 40 °C. The solid was filtered off under vacuum and washed with diethyl ether to give the *title compound* **(3)** as a white powder (0.75 g, 57 % based on C elemental analysis assuming 2.5 ethoxy groups have eliminated)); ν_{max} (KBr disc) 3408 (OH), 2980 (CH_2), 1637 (H_2O), 1051 (Si-O-Si), 948 (Si-O-Si), 795 (Si-O-Si) Found C, 9.37; H, 1.93; N, 0.00 %, (Calc. C, 16.50; H, 2.92; N, 0.00 % (N % proves no N incorporation) for an average of 2.5 ethoxy groups eliminating and based on calculated from amount of silane used - See Appendix 6.2); Loading = 2.0 ± 0.2 mmol g^{-1} (From % C).

N-Acetyl aminopropyl- functionalised MCM-41 **(4)**



In ether (3 ml) aminopropyl functionalised MCM-41 **(2)** (200 mg, 0.36 mmol of N) and triethylamine (112 μl, 0.8 mmol) were added and the mixture was stirred under nitrogen. Acetic anhydride (0.26 ml, 2.76 mmol) was added dropwise and the reaction was stirred at room temperature. After an hour, the Kaiser test for free amines was negative and the reaction stopped.[3] The product was filtered and washed with ether and dried overnight under vacuum to give the *title compound* **(4)** as a white powder (74 % by N elemental analysis and 78 % by C elemental analysis). ν_{max} (KBr disc) 3382 (OH), 2981 (CH), 1635 (H_2O), 1558 (CO) 1045 (Si-O- Si), 803 (Si-O-Si); Found C, 10.37; H, 2.11; N, 1.91 %, (Calc. C, 13.25; H, 2.30; N, 2.58 %); δ_c (MSL) –0.5 ($SiCH_3$), 8.2 ($SiCH_2$), 16.3 (CH_2CH_3), 22.3 ($COCH_3$), 42.1 ($CH_2CH_2CH_2$), 47.1 (CH_2N), 59.6 (OCH_2) 172.9 (CO). Loading = 1.4 ± 0.2 mmol g^{-1}.

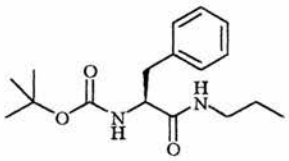
Boc–L–phenylalanine pentafluorophenyl ester **(5)**



The title compound was prepared using the procedure described by Kisfaludy and co-workers.[3] To an ice-cold solution of Boc–L–phenylalanine (1.33 g, 5 mmol) in dioxane (2.5 ml) and DMF (2.5 ml), pentafluorophenol (1.05 g, 5.5 mmol) and DCC (1.19 g, 5.5 mmol) were added and the mixture was stirred for two hour at 0 °C. The white precipitate was filtered off and the filtrate was evaporated to dryness. The residue was triturated with n-hexane and filtered to give a white solid which was purified by recrystallisation to give the *title compound* **(5)** as white crystals. (1.53 g, 76 %); m.p. 110-112 °C (hexane-ethyl acetate), (lit., 111-112 °C[9]); $[\alpha]_D$ -14.1 (c 1,

dioxane), (lit., –26.9 [9]); $\delta_H(CDCl_3)$ 1.43 (9 H, s, t-Bu), 3.24 (2 H, m, C*H*$_2$Ph), 4.94 (1 H, m, C*H*NH), 7.23-7.38 (5 H, m, Aromatic H); δ_F ($CDCl_3$) -153.02 (2F, d, *J* 20, *o*-F), -158.69 (2F, t, *J* 22, *m*-F), -163.39 (1F, dd, *J* 22, *J* 19, *p*-F); δ_C ($CDCl_3$) 28.2 (CH_3), 37.3 (*C*HNH), 54.4 (*C*H$_2$Ph), 80.7 (C quat.), 127.6, 129.0, 129.4, 135.0 (aromatic C), 139.4, 139.6, 141.5, 142.8 (aromatic C), 155.1 (CO), 168.6 (CO).

Boc-L-phenylalanine propylamide **(6)**

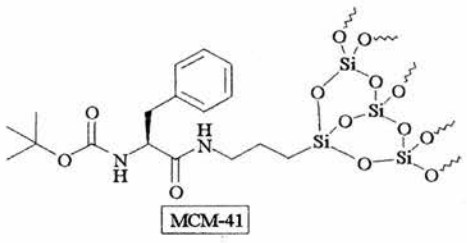


Method 1: The title compound was prepared using the procedure described by Kisfaludy and co-workers.[3] *N*-Propylamine (40.9 mg, 0.69 mmol) and sodium hydrogen carbonate (94 mg, 1.12 mmol) were added together in acetone (1.3 ml) and water (2.4 ml). Boc-L-phenylalanine pentafluorophenyl ester (106 mg, 0.24 mmol) was added and the mixture stirred at room temperature for 24 hours. The product was extracted with ethyl acetate (3 x 10 ml). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was triturated with n-hexane and then crystallised from ethyl acetate/ hexane and then recrystallised from ethanol/ water to give the slightly impure *title compound* **(6)**; (37 mg, 55 %); See method 2 for characterisation data.

Method 2: The title compound was prepared using the procedure described by Castro and co-workers.[4] In acetonitrile (2.5 ml), propylamine (22 mg, 0.38 mmol), Boc-L-phenylalanine (100 mg, 0.38 mmol) and PyBOP (196 mg, 0.38 mmol) were added and stirred. DIEA (114 mg, 0.88 mmol) was added and the mixture was stirred at room temperature for two hours. The volume was reduced to 0.5 ml and ethyl acetate

(10 ml) was added. The organic phase was washed with 3M HCl solution, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution and then the organic phase was dried over magnesium sulphate. The solvent was evaporated off and the residue crystallised to give the slightly impure *title compound* **(6)**; (49 mg, 62 %); $[\alpha]_D$ 20.6 (c 1, chloroform); δ_H ($CDCl_3$), 0.77 (3 H, t, *J* 7, CH_2CH_3), 1.29 (2 H, m, CH_2CH_3), 1.40 (9 H, s, CH_3), 3.05 (4 H, m, $NHCH_2$ and $PhCH_2$), 4.32 (1 H, br. s, CH), 5.32 (1 H, br. s, NH), 6.02 (1 H, br. s, NH), 7.16 – 7.26 (5 H, m, Ph); δ_C ($CDCl_3$) 11.1 (CH_3), 22.4 (CH_2), 28.1 (3 x CH_3), 38.8 ($NHCH_2$), 41.0 (NHCH), 55.9 ($PhCH_2$), 79.9 (Boc C quat.), 126.8, 128.6, 129.4, (Ph), 137.1 (Ph C quat.), 155.6, 171.4 (2 x CO); ν_{max} (Nujol) 3341 (CONH), 2855 (CH), 1749 (OCO), 1656 (CON); Found C, 66.74; H, 8.61; N 8.74 %; (Calc. C, 66.64; H, 8.55; N, 9.14 %);

Boc-L-Phenylalaninyl amidopropyl functionalised MCM-41 **(7)**

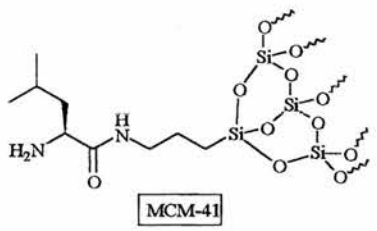


Method 1: The procedure for the synthesis of the *title compound* **(7)** was adapted from a procedure described by Kisfaludy and co-workers.[3] Aminopropyl functionalised MCM-41 **(2)** (50 mg, loading = 1.8 mmol g^{-1}) and Boc-Phenylalanine pentafluorophenyl ester (86 mg, 0.20 mmol) were added together in acetonitrile (2.5 ml). To the mixture DIEA (58 mg, 0.45 mmol) was added and the mixture was stirred overnight. The product was washed well with acetonitrile, until TLC showed no by-products in the eluant, to give the *title compound* **(7)** (64 % by N elemental analysis and 52 % by C elemental analysis); ν_{max} (KBr disc) 3410 (OH), 2983 (CH_2),

1697, 1654 (CO), 1074 (Si-O-Si), 961 (Si-O-Si), 796 (Si-O-Si); Found C, 20.81; H, 2.80; N 3.29 %; (Calc. C, 39.74; H, 5.06; N, 5.15 %); Loading = 1.2 ± 0.1 mmol g^{-1}.

Method 2: The title compound **(7)** was prepared using a modified procedure described by Castro and co-workers. Aminopropyl functionalised MCM-41 **(2)** (50 mg, loading = 1.8 mmol g^{-1}), Boc-Phenylalanine (53 mg, 0.20 mmol) and PyBOP (104 mg, 0.20 mmol) were added together in acetonitrile (2.5 ml). To the mixture DIEA (88 ml, 0.50 mmol) was added and the mixture was stirred for 3 hrs. The product was washed well with acetonitrile, until TLC showed no by-products in the eluant, to give the *title compound* **(7)** (71 % by N elemental analysis and 54 % by C elemental analysis); ν_{max} (KBr disc) 3400 (OH), 2958 (CH_2), 1694, 1656 (CO), 1128 (Si-O-Si), 968 (Si-O-Si), 797 (Si-O-Si); Found C, 21.57; H, 2.98; N, 3.67 %, (Calc. C, 39.74; H, 5.06; N, 5.15 %); Loading = 1.3 ± 0.1 mmol g^{-1}.

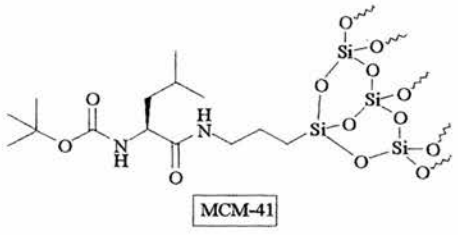
L-Leucinyl amidopropyl functionalised MCM-41 **(8)**



The title compound **(8)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised MCM-41 **(2)** (100 mg, loading = 1.8 mmol g^{-1}) was added to dry acetonitrile (5 ml). Boc-L-leu (87 mg, 0.40 mmol) and PyBOP (120 mg, 0.23 mmol) were added and finally DIEA (150 µl, 0.5 mmol). The mixture was stirred overnight at room temperature. The solid was filtered off under vacuum and washed with acetonitrile and then diethyl ether to give the product as a white powder, which was dried under vacuum overnight. The product was mixed

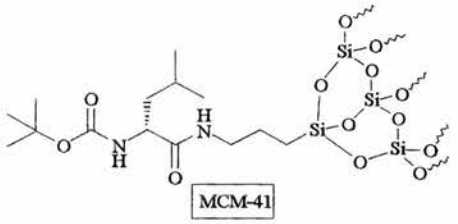
with TFA/DCM (2 ml 1:1) and then filtered and washed with DCM followed by diethyl ether and dried under vacuum to give the *title compound* **(8)**. (45 % by N elemental analysis and 52 % by C elemental analysis), ν_{max} (KBr disc) 3436 (OH), 2958 (CH_2), 1654 (H_2O), 1540 (CO), 1047 (Si-O-Si), 954 (Si-O-Si), 798 (Si-O-Si); Found C, 13.46; H, 2.30; N, 2.32 %; (Calc. C, 25.76; H, 3.96; N, 5.15 %) Loading = 0.8 ± 0.1 mmol g^{-1}.

Boc – L – Leucinyl amidopropyl functionalised MCM-41 **(9)**.



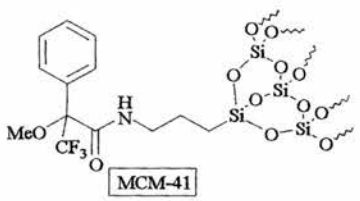
The title compound **(9)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised MCM-41 **(2)** (100 mg, loading = 1.8 mmol g^{-1}) was added to dry acetonitrile (5 ml). Boc-L-leu (87 mg, 0.40 mmol) and PyBOP (240 mg, 0.46 mmol) were added and finally DIEA (150 µl, 0.5 mmol). The mixture was stirred for 2 days at room temperature until the Kaiser test for free amines was negative. The solid was filtered off under vacuum and washed with acetonitrile and then diethyl ether to give the *title compound* **(9)** as a white powder. (57 % by N elemental analysis and 39 % by C elemental analysis); ν_{max} (KBr disc) 3393 (OH), 2963 (CH), 1707 (CO), 1652 (CO) 1088 (Si-O-Si), 802 (Si-O-Si); δ_c (MSL) –0.5 ($SiCH_3$), 9.8 ($SiCH_2$), 18.1 (CH_2CH_3, $CH_2CH_2CH_2$), 21.7 ($CH(CH_3)_2$), 25.0 ($CH(CH_3)_2$), 27.9 (3 x CH_3), 41.8 ($CHCH_2$, CH_2N), 54.1 (NCH), 58.6 ($OCMe_3$) 172.9, 158.2 (CO); Found C, 15.13; H, 2.75; N, 2.91 %, (Calc. C, 38.64; H, 5.43; N, 5.15 %); Loading = 1.0 ± 0.1 mmol g^{-1}.

Boc – D – Leucinyl amidopropyl functionalised MCM-41 **(10)**.



The title compound **(10)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised MCM-41 **(2)** (100 mg, loading = 1.8 mmol g^{-1}) was added to dry acetonitrile (5 ml). Boc-D-leu (87 mg, 0.40 mmol) and PyBOP (240 mg, 0.46 mmol) were added and finally DIEA (150 µl, 0.5 mmol). The mixture was stirred for 2 days at room temperature until the Kaiser test for free amines was negative. The solid was filtered off under vacuum and washed with acetonitrile and then diethyl ether to give the *title compound* **(10)** as a white powder. (52 % by N elemental analysis and 39 % by C elemental analysis); ν_{max} (KBr disc) 3395 (OH), 2970 (CH), 1701 (CO), 1653 (CO) 1078 (Si-O-Si), 798 (Si-O-Si); Found C, 14.89; H, 2.78; N, 2.66 %; (Calc. C, 38.64; H, 5.43; N, 5.15 %); Loading = 1.0 ± 0.1 mmol g^{-1}.

(S) *Methoxy-(phenyl)-trifluoromethylacetamido amidopropyl functionalised MCM-41 (Mosher's acid propylamide functionalised MCM-41)* ***(11)***

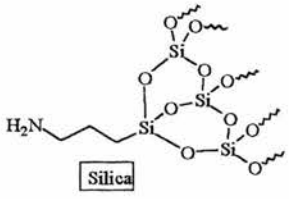


Freshly distilled (S) Mosher's acid chloride (74 µm, 0.42 mmol) and aminopropyl functionalised MCM-41 **(2)** (106 mg, loading = 1.8 mmol g^{-1}) were mixed together in acetonitrile (3 ml). DIEA (0.1 ml, 0.53 mmol) was added and the mixture stirred overnight. The product was washed with ether to give the *title compound* **(11)** (91 %

by N elemental analysis and 68 % by C elemental analysis); ν_{max} (KBr disc) 3384 (OH), 2949 (CH_2), 1679 (CO), 1534 (H_2O), 1122 (Si-O-Si), 959 (Si-O-Si), 802 (Si-O-Si); Found C, 20.87; H, 2.70; N, 2.34 %, (Calc. C, 30.91; H, 3.22; N, 2.58 %); Loading = 1.7 ± 0.2 mmol g^{-1}.

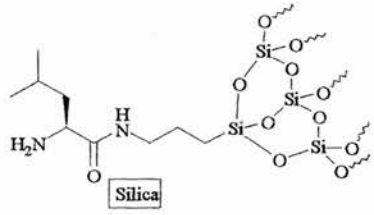
2.2.2 Inorganic Organic Hybrids Based On Silica.

Aminopropyl functionalised silica **(12)**



The same procedure as for the aminopropyl-functionalised MCM-41 **(2)** was employed except silica (0.65 g) instead of MCM-41 **(1)** was used to give the *title compound* **(12)** as a white powder (0.66 g) 29 % from N elemental analysis, calculated from amount of silane used); ν_{max} (KBr disc) 3319 (OH), 2945 (CH_2), 1652 (H_2O), 1025 (Si-O-Si), 795 (Si-O-Si) Found C, 4.83; H, 1.29; N, 1.40 %, (Calc. C, 16.50; H, 2.92; N, 4.81 % for an average of 2.5 ethoxy groups eliminating and based on calculated from amount of silane used (See Appendix 6.2); Loading = 1.0 ± 0.2 mmol g^{-1}.

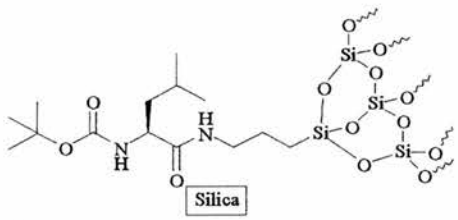
L-leucinyl amidopropyl functionalised Silica **(13)**



The title compound **(13)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised Silica (100 mg, Fluka loading 1.0 mmol g^{-1}) was added to dry acetonitrile (5 ml). Boc-L-leu (57 mg, 0.26 mmol)

and PyBOP (72 mg, 0.14 mmol) were added and finally DIEA (88 μl, 0.29 mmol). The mixture was stirred overnight at room temperature until the Kaiser test for free amines was negative. The solid was filtered off under vacuum and washed with acetonitrile and then diethyl ether to give the product as a white powder, which was dried under vacuum overnight. The product was then mixed with TFA / DCM (2 ml 1:1) and then filtered and washed with DCM followed by diethyl ether and dried in a vacuum to give the *title compound* **(13)**. (70 % by N elemental analysis and 84 % by C elemental analysis); ν_{max} (KBr disc) 3436 (OH), 2968 (CH_2), 1685 (CO), 1538 (H_2O), 1094 (Si-O-Si), 954 (Si-O-Si), 793 (Si-O-Si); Found C, 10.06; H, 1.81; N, 1.96 %, (Calc. C, 12.00; H, 2.15; N, 2.8 %); Loading = 0.7 ± 0.1 mmol g^{-1}.

Boc-L-leucinyl amidopropyl functionalised Silica **(14)**



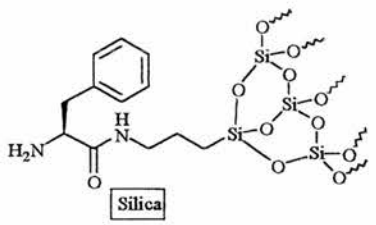
The title compound **(14)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised Silica (1 g, Fluka loading 1.0 mmol g^{-1}) was added to dry acetonitrile (50 ml). Boc-L-leu (800 mg, 3.48 mmol) and PyBOP (1.81 g, 3.475 mmol) were added and finally DIEA (1.7 ml, 4 mmol). The mixture was stirred overnight at room temperature until the Kaiser test for free amines was negative. The solid was filtered off under vacuum and washed with acetonitrile and then diethyl ether and then dried under vacuum overnight to give the *title compound* **(14)**; (89 % by N elemental analysis and 68 % by C elemental analysis); ν_{max} (KBr disc) 3353 (OH), 2984 (CH), 1652 (CO) 1044 (Si-O-Si), 798 (Si-O-Si); δ_c 10.7 ($SiCH_2$), 22.2, 24.9, 27.7 ($CH_2CH_2CH_2$, $CH(CH_3)_2$, 3 x CH_3), 44.3

(CH_2N), 53.8 (NCH), 157.5, 174.7 (CO); Found C, 12.20; H, 2.19; N, 2.48 %, (Calc. C, 18.00; H, 2.95; N, 2.80 %); Loading = 0.9 ± 0.1 mmol g^{-1}.

Boc-L-Phenylalaninyl amidopropyl functionalised Silica **(15)**

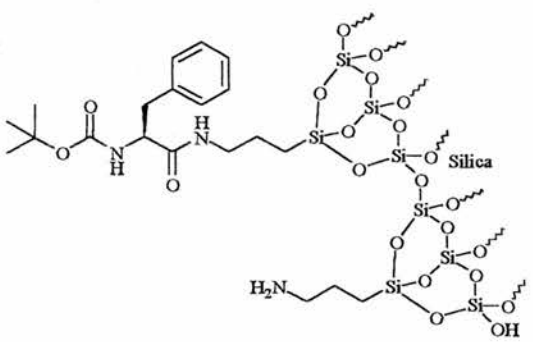
The title compound **(15)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised Silica (1 g, Fluka, loading 1.0 mmol g^{-1}) was added to dry acetonitrile (50 ml). Boc-L-Phe (920 mg, 3.48 mmol) and PyBOP (1.81 g, 3.475 mmol) were added and finally DIEA (1.7 ml, 4 mmol). The mixture was stirred overnight at room temperature until the Kaiser test for free amines was negative. The solid was filtered off under vacuum and washed with acetonitrile and then diethyl ether and then dried under vacuum overnight to give the *title compound* **(15)**; (97 % by N elemental analysis and 68 % by C elemental analysis); ν_{max} (KBr disc) 3325 (OH), 2994 (CH), 1673 (CO) 1093 (Si-O-Si), 801 (Si-O-Si); δ_c 11.1 ($SiCH_2$), 22.4, ($CH_2CH_2CH_2$), 27.4 (3 x CH_3), 44.2 (CH_2N, CH_2Ar), 57.1 (NCH), 128.4 (Ph), 157.3, 174.4 (CO); Found C, 14.62; H, 2.18; N, 2.71 %, (Calc. C, 21.6; H, 2.75; N, 2.80 %); Loading = 1.0 ± 0.1 mmol g^{-1}.

L-Phenylalaninyl amidopropyl functionalised Silica **(16)**



The title compound **(16)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised Silica (1 g, Fluka, loading 1.0 mmol g^{-1}) was added to dry acetonitrile (50 ml). Boc-L-Phe (920 mg, 3.48 mmol) and PyBOP (1.81 g, 3.475 mmol) were added and finally DIEA (1.7 ml, 4 mmol). The mixture was stirred overnight at room temperature until the Kaiser test for free amines was negative. The product was then mixed with TFA/DCM (2 ml 1:1) and filtered and washed with DCM followed by diethyl ether and dried in a vacuum to give the *title compound* **(13)**. (95 % by N elemental analysis and 70 % by C elemental analysis); ν_{max} (KBr disc) 3440 (OH), 2928 (CH_2), 1645 (CO), 1090 (Si-O-Si), 955 (Si-O-Si), 794 (Si-O-Si); Found C, 10.08; H, 2.01; N, 2.66 %, (Calc. C, 14.40; H, 1.7; N, 2.8 %); Loading = 1.0 ± 0.2 mmol g^{-1}.

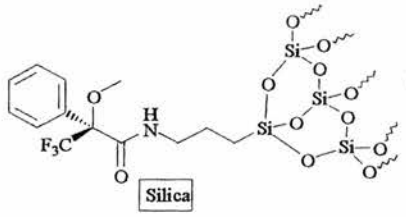
50 % Derivatised Boc-L-Phenylalaninyl amidopropyl functionalised Silica **(16)**



The title compound **(16)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised Silica (1 g, ~1.0 mmol N/ g) was added to dry acetonitrile (50 ml). Boc-L-Phe (184 mg, 0.70 mmol) and PyBOP (367 mg, 0.70 mmol) were added and finally DIEA (0.3 ml, 1 mmol). The mixture was stirred overnight at room temperature. The solid was filtered off under vacuum and washed with acetonitrile and then diethyl ether and then dried under vacuum overnight to give the *title compound* **(16)**. (118 % by N elemental analysis and 96 % by C elemental analysis); ν_{max} (KBr disc) 3326 (OH), 2955 (CH), 1658 (CO) 1055

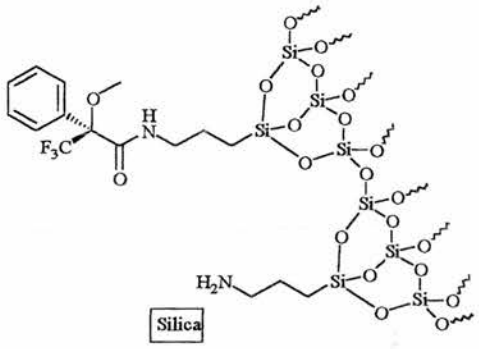
(Si-O-Si), 800 (Si-O-Si); δ_c (MSL) 9.7 ($SiCH_2$), 22.6, ($CH_2CH_2CH_2$), 27.2 (3 x CH_3), 42.1 (CH_2N, CH_2Ar), 56.8 (NCH), 128.4 (Ph), 157.3, 175.9 (CO); Found C, 12.62; H, 1.85; N, 2.47 %, (Calc. C, 13.20; H, 1.90; N, 2.10 %); Loading = 0.6 ± 0.1 mmol g^{-1}.

(S) – Methoxy (phenyl) trifluoromethyl acetamido amidopropyl functionalised Silica **(17)**



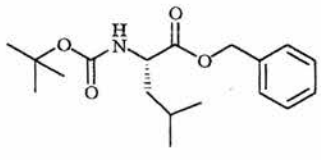
The title compound **(17)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised Silica (0.5 g, Fluka, loading = 1.0 mmol g^{-1}) was added to dry acetonitrile (20 ml). (S)- Mosher's acid (325 mg, 1.39 mmol) and PyBOP (750 mg, 1.39 mmol) were added and finally DIEA (0.6 ml, 2 mmol). The mixture was then stirred for three days at room temperature until the Kaiser test for free amines was negative. The solid was filtered off under vacuum and washed with acetonitrile and then diethyl ether and dried under vacuum overnight to give the *title compound* **(17)**. (148 % by N elemental analysis and 70 % by C elemental analysis); ν_{max} (KBr disc) 3314 (OH), 2950 (CH), 1669 (CO) 1032 (Si-O-Si), 795 (Si-O-Si); δ_c (MSL) 9.9 ($SiCH_2$), 22.2, ($CH_2CH_2CH_2$), 42.6 (CH_2N), 52.9 (OMe), 84.4 (CF_3), 127.7 (Ph), 167.5 (CO); Found C, 11.83; H, 1.25; N, 2.07 %, (Calc. C, 16.80; H, 1.75; N, 1.40 %); Loading = 1.5 ± 0.2 mmol g^{-1}.

50 % Derivatised (S) – Methoxy (phenyl) trifluoromethyl acetamido amidopropyl functionalised Silica **(18)**



The title compound **(18)** was prepared using a modified procedure described by Castro and co-workers.[4] Aminopropyl functionalised Silica (0.5 g, ~1.0 mmol N/ g) was added to dry acetonitrile (20 ml). (S)- Mosher's acid (81 mg, 0.25 mmol) and PyBOP (400 mg, 0.74 mmol) were added and finally DIEA (0.3 ml, 1 mmol). The mixture was then stirred for three days at room temperature. The solid was filtered off under vacuum and washed with acetonitrile and then diethyl ether and dried under vacuum overnight to give the *title compound* **(18)**. (151 % by N elemental analysis and 107 % by C elemental analysis); ν_{max} (KBr disc) 3259 (OH), 2990 (CH), 1622 (CO) 1005 (Si-O-Si), 791 (Si-O-Si); δ_c (MSL) 10.3 ($SiCH_2$), 22.6, ($CH_2CH_2CH_2$), 42.3 (CH_2N), 53.4 (OMe), 84.6 (CF_3), 128.1 (Ph), 168.2 (CO); Found C, 11.57; H, 1.31; N, 2.12 %, (Calc. C, 10.80; H, 2.8; N, 1.40 %); Loading = 0.5 ± 0.1 mmol g^{-1}.

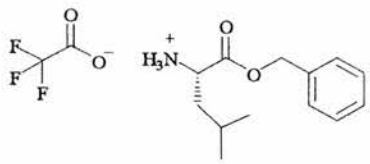
Boc-L-Leucine benzyl ester **(20)**



The title compound **(20)** was prepared using the procedure described by Sugawara and co-workers.[10] In acetonitrile (20 ml), Boc-L-leucine (1 g, 4.3 mmol), silver

carbonate (800 mg, 4.76 mmol) and benzyl bromide (0.56 ml, 4.76 mmol) were mixed together and the mixture was stirred for 24 hours in the dark. Once all the starting material had disappeared, as judged by TLC (Hexane: EtOAc, 4:1), methanol (1.5 ml) was added to quench the excess benzyl bromide. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The product was purified by column chromatography (Hexane: EtOAc, 4:1) to give the *title compound* **(20)** as a pale yellow oil. (1.02 g, 74 %); $[\alpha]_D$ – 35 (c 1, methanol) (Lit[10] - 38); δ_H ($CDCl_3$), 0.91 (3 H, d, *J* 6, CH_3), 0.92 (3 H, d, *J* 6, CH_3), 1.43 (9 H, s, $C(CH_3)_3$), 1.70 - 1.46 (3 H, m, CH and CH_2), 4.36 (1 H, m, α CH), 4.93 (1 H, bs, NH), 5.12 (1 H, d, *J* 18, OCH_2), 5.18 (1 H, d, *J* 18, OCH_2), 7.38-7.26 (5 H, m, Ph); δ_C ($CDCl_3$) 21.8, 22.8 (2 x CH_3), 24.7 (Me_2CH), 28.3 (3 x CH_3), 41.7 (CH_2), 52.2 (CHN), 66.9 (OCH_2), 79.8 (C quat.), 128.3, 128.4, 128.7 (CH (Ph)), 135.7 (C quat. (Ph)), 155.6 (NCO), 175.5 (OCO); ν_{max} (thin film) 3373 (CONH), 2960 (CH), 1718 (CO); m/z (CI +ve) 322.202487 ($M + H^+$) ($C_{18}H_{28}NO_2$ requires 322.201834).

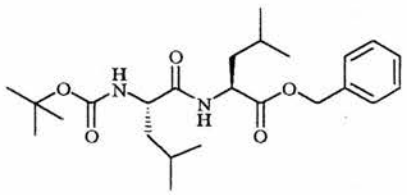
L-Leucine benzyl ester (trifluoroacetic acid salt) **(21)**



The title compound was prepared using the procedure described by Sugawara and co-workers.[10] Boc-L-leucine benzyl ester **(20)** was dissolved in DCM/ TFA (10 ml, 1:1) and stirred for 30 minutes. The product **(21)** was obtained by repeated co – evaporations with *iso*propanol in quantitative yields as an oil (product was taken on to coupling step with no further purification); δ_H ($CDCl_3$), 0.91 (3 H, d, *J* 6, CH_3), 0.92 (3 H, d, *J* 6, CH_3), 1.72 - 1.78 (3 H, m, CH and CH_2), 4.10 (1 H, m, α CH), 5.14 (1 H, d, *J* 19, OCH_2), 5.18 (1 H, d, *J* 19, OCH_2), 7.89 - 7.26 (5 H, m, Ph), 8.07 (3 H,

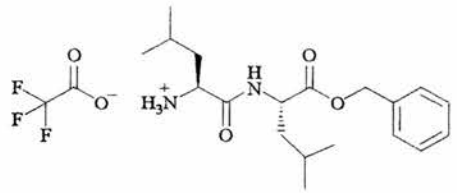
bs, NH_3^+); δ_C ($CDCl_3$) 21.5, 21.8 (2 x CH_3), 24.3 (Me_2CH), 39.3 (CH_2), 52.1 (CHN), 68.7 (OCH_2), 112.5 (CF_3 multiplet), 128.6, 128.9, 129.1 (CH (Ph)), 134.2 (C quat. (Ph)), 161 (CO), 170.2 (CON); δ_F ($CDCl_3$) -76.85 (CF_3); ν_{max} (thin film) 3052 (NH_3^+), 2967 (CH), 1746, 1672 (CO), 1175 (CF_3); m/z (CI +ve) 222.149882 (M + H^+) ($C_{13}H_{20}NO_2$ requires 222.149404).

Boc – L – leucinyl – L – leucine benzyl ester **(22)**



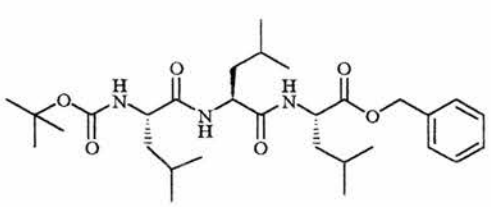
The title compound was prepared using the procedure described by Castro and co-workers.[4] In acetonitrile (50 ml), Boc-L-leucine (1.6 g, 7 mmol), L-leucine benzyl ester **(21)** (1.07 g, 3.2 mmol) and PyBOP (1.5 g, 7 mmol) were added together. DIEA (1.8 ml, 10 mmol) was added and the mixture stirred for two hours at room temperature. The solvent was evaporated off and the residue was purified by column chromatography (Hexane: EtOAc 4:1) to give the *title compound* **(22)** as a white solid. (1.00 g, 75 %); m.p. 80-83 °C (hexane / ethyl acetate) (Lit.[11] 82 – 85 °C); $[\alpha]_D$ - 49 (c 1, chloroform) (Lit[11] - 48); δ_H ($CDCl_3$), 0.89 - 0.91 (12 H, m, 4 x CH_3), 1.42 (9 H, s, $C(CH_3)_3$), 1.43 - 1.68 (6 H, m, 2 x CH and 2 x CH_2), 4.10 (1 H, m, α CH), 4.65 (1 H, m, α CH), 4.90 (1 H, bd, *J* 8, NH), 5.14 (1 H, d, *J* 15, OCH_2), 5.18 (1 H, d, *J* 15, OCH_2), 6.47 (1 H, bd, *J* 8, NH), 7.26-7.36 (5 H, m, Ph); δ_C ($CDCl_3$) 21.8, 22.8 (4 x CH_3), 24.6 (2 x Me_2CH), 28.2 (3 x CH_3), 40.8, 41.4 (2 x CH_2), 50.8, 53.0 (2 x CHN), 67.1 (OCH_2), 80.3 (C quat.), 128.3, 128.5, 128.7 (CH (Ph)), 135.5 (C quat. (Ph)), 172.4, 172.5, 172.7 (3 x CO) ν_{max} (KBr Disc) 3363 (CONH), 2953 (CH), 1725 (CO); m/z (CI +ve) 435.284693 (M + H^+) ($C_{24}H_{39}N_2O_5$ requires 435.285898).

L- -leucinyl – L - leucine benzyl ester (trifluoroacetic acid salt) **(23)**



The title compound was prepared using the procedure described by Sugawara and co-workers.[10] Boc-L-leucinyl-L-leucine benzyl ester **(22)** was dissolved in DCM/ TFA (10 ml, 1:1) and stirred for 30 minutes. The product **(23)** was obtained by repeated co – evaporations with *iso*propanol in quantitative yields as an oil (product was taken on to coupling step with no further purification); δ_H ($CDCl_3$), 0.82 - 0.86 (12 H, m, 4 x CH_3), 1.60 - 1.66 (6 H, m, 2 x CH and 2 x CH_2), 4.15 (1 H, m, α CH), 4.46 (1 H, m, α CH), 5.11 (1 H, d, *J* 20, OCH_2), 5.16 (1 H, d, *J* 20, OCH_2), 7.26 - 7.35 (5 H, m, Ph), 7.58 (1 H, bd, *J* 7, NH), 8.01 (3 H, bs, NH_3^+); δ_C ($CDCl_3$) 21.5, 21.9, 22.3 (4 x CH_3), 24.1, 24.5 (2 x Me_2CH), 40.3, 40.6 (2 x CH_2), 51.9, 52.3 (2 x CHN), 67.4 (OCH_2), 112.5 (CF_3 multiplet), 128.4, 128.7, 128.7 (CH (Ph)), 135.2 (C quat. (Ph)), 161.8 (CO_2 (multiplet)), 169.8, 172.1 (2 x CO); δ_F ($CDCl_3$) -76.74 (CF_3); ν_{max} (Thin Film) 3356 (CONH), 3048 (NH_3^+), 2964 (CH), 1731, 1672 (CO), 1176 (CF_3); m/z (CI +ve) 335.234344 ($M + H^+$) ($C_{19}H_{31}N_2O_3$ requires 332.233468).

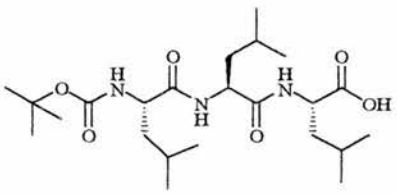
Boc – L – leucinyl – L – Leucinyl – L – Leucine benzyl ester **(24)**



The title compound was prepared as for Boc-L-leucinyl-L-Leucine benzyl ester **(21)** except L-leucinyl-L-leucine benzyl ester (trifluoroacetic acid salt) **(23)** (1.00 g, 2.23 mmol) was used instead of L-leucine benzyl ester (1.07 g, 3.2 mmol) to give the *title*

compound **(24)** as an off white solid. (0.98 g, 80 %); m.p. 138 - 140 °C (hexane / ethyl acetate) (Lit.[10] 140.5 - 141.5 °C); $[\alpha]_D$ - 68 (c 1, methanol) (Lit.[10] - 69.5); δ_H ($CDCl_3$), 0.86 - 0.93 (18 H, m, 6 x CH_3), 1.42 (9 H, s, $C(CH_3)_3$), 1.44 - 1.68 (9 H, m, 3 x CH and 3 x CH_2), 4.10 (1 H, m, α CH), 4.43 (1 H, m, α CH), 4.65 (1 H, m, α CH), 4.90 (1 H, bd, *J* 8, NH), 5.11 (1 H, d, *J* 17, OCH_2), 5.17 (1 H, d, *J* 17, OCH_2), 6.52 (3 H, m, 3 x NH), 7.26 - 7.35 (5 H, m, Ph); δ_C ($CDCl_3$) 21.8, 21.9, 22.7, 22.8 (6 x CH_3), 24.5, 24.7 (3 x Me_2CH), 28.2 (3 x CH_3), 40.6, 40.9, 41.3 (3 x CH_2), 50.9, 51.6, 53.1 (3 x CHN), 67.1 (OCH_2), 80.1 (C quat.), 128.4, 128.7, 128.7 (CH (Ph)), 135.5 (C quat. (Ph)), 171.7, 172.6, 172.8 (4 x CO) ν_{max} (KBr Disc) 3367 (CONH), 2962 (CH), 1719 (CO); m/z (CI +ve) 547.363349 (M^+) ($C_{30}H_{49}N_3O_6$ requires 547.362137).

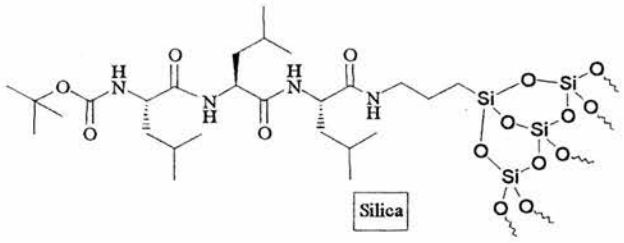
Boc – L – leucinyl – L – Leucinyl – L – Leucine **(25)**



The title compound was prepared using the procedure described by Narita and co-workers.[12] In acetic acid (50 ml) Boc-L-leucinyl-L-Leucinyl-L-Leucine benzyl ester **(24)** (1 g) and 10 % Pd/C (200 mg) were added together and the mixture put under an atmosphere of hydrogen. The reaction was stirred overnight. The mixture was filtered through Celite and the solvent was removed by co - evaporation with toluene to give the *title compound* **(25)** as an off white solid in quantitative yields; $[\alpha]_D$ – 81.6 (c 1, methanol); δ_H ($CDCl_3$), 0.86 - 0.93 (18 H, m, 6 x CH_3), 1.42 (9 H, s, $C(CH_3)_3$), 1.46 - 1.69 (9 H, m, 3 x CH and 3 x CH_2), 4.11 (1 H, m, α CH), 4.54 (1 H, m, α CH), 4.56 (1 H, m, α CH), 5.07 (1 H, bd, *J* 8, NH), 7.01 - 7.13 (3 H, m, 3 x

NH); δ_C ($CDCl_3$) 26.8, 22.0, 22.9 (6 x CH_3), 24.6, 24.7, 24.8 (3 x Me_2CH), 28.3 (3 x CH_3), 40.7, 40.9, 41.1 (3 x CH_2), 51.1, 51.9, 53.2 (3 x CHN), 80.3 (C quat.), 155.9 (CO_2H), 172.1, 173.1, 175.7 (4 x CO) ν_{max} (KBr Disc) 3367 (CONH), 2962 (CH), 1719 (CO); m/z (CI +ve) 458.322046 ($M + H^+$) ($C_{23}H_{44}N_3O_6$ requires 458.323012).

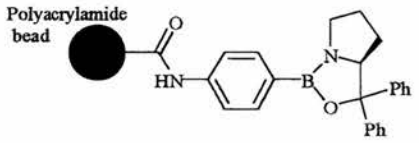
Boc – L – leucinyl – L – Leucinyl – L – Leucinyl amidopropyl functionalised Silica **(26)**



The title compound was prepared using the procedure described by Castro and co-workers.[4] In acetonitrile (20 ml), Boc-L-leucinyl-L-Leucinyl-L-Leucine **(25)** (400 mg, 0.86 mmol), aminopropyl functionalised silica (250 mg, ~1 mmol/g N) and PyBOP (338 mg, 0.65 mmol) were added together. DIEA (0.113 ml, 0.65 mmol) was added and the mixture stirred for 24 hours at room temperature. The product was filtered and washed with acetonitrile, DCM and ether to give the *title compound* **(26)** as a white solid, (56 % by N elemental analysis and 34 % by C elemental analysis); ν_{max} (KBr disc) 3449 (OH), 2974 (CH_2), 1659 (CO), 1094 (Si-O-Si), 799 (Si-O-Si); Found C, 13.24; H, 2.5; N, 3.15 %. (Calc. C, 38.40; H, 6.65; N, 5.60 %); Loading = 0.6 ± 0.1 mmol g^{-1}.

2.2.3 Synthesis of Solid Supported Oxazaborolidines

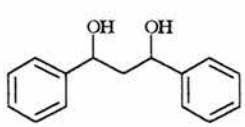
2.2.3.1 Polymer Bound Oxazaborolidine (27).



The title compound was prepared using a modified procedure described by Giffels and co-workers.[7] In toluene (10 ml), Polyacrylamide supported boronic acid (Pierce, 100 μmol B per ml, in water) (3 ml, 0.3 mmol boronic acid) and (S)-α,α-diphenyl prolinol (114 mg, 0.45 mmol) were added together and the mixture refluxed with a Dean-Stark apparatus for 4 hours. The solid was then filtered and washed with toluene and then ether and dried to give the *title compound* **(27)** as a cream solid; 0.4811 g, 98 % (by increase of weight), δ_C (MSL) 41.6 (CH's, very br. s from 20 ppm to 52 ppm), 118.0, 129.5, 138.0 (Ph), 179.4 (CO); δ_B (MSL) 4.35 (B); ν_{max} (KBr disc) 3430 (CONH), 2924 (CH_2), 1782 (CO), 1519 (B-O), 1305 (B-N); Found C, 48.24; H, 6.85; N, 15.81 %, (Elemental analysis before reaction C, 46.77; H, 7.09; N, 15.59 % Increase of C, 1.47, N, 0.22 % (17 % by N elemental analysis and 22 % by C elemental analysis)).

2.2.3.2 Silicate Supported Oxazaborolidine.

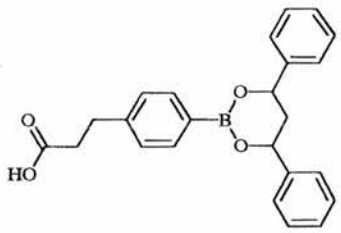
1,3 Diphenylpropane - 1,3 - diol **(28)**



The known title compound was prepared using a procedure described by Tiecco and co-workers.[13] In ethanol (10 ml), dibenzoylmethane (2 g, 9 mmol) and sodium borohydride (1.72 g, 45 mmol) were added together and the mixture was stirred at room temperature for 3 hours. Hydrochloric acid (2 N, 20 ml) was added dropwise

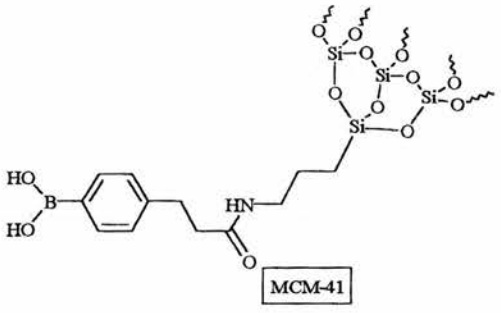
followed by water (5 ml). The mixture was stirred for 15 min and the layers were separated. The organic phase was washed with sodium bicarbonate solution (3 x 10 ml) and the organic phase was dried over magnesium sulphate. The product was purified by column chromatography (*i*-hexane: ethyl acetate 4:1) to give the *title compound* **(28)** as a white solid; 1.59 g, 76 %; m.p. 124 – 125 °C (Lit.[14] 123 °C), δ_H ($CDCl_3$) 2.12 (m, 2 H, $CHCH_2$), 2.95, 3.38 (2 x s, 2 H, OH, diastereoisomers ratio 2:1 trans: cis), 5.16 (m, 2 H, 2 x CH), 7.31 (m, 10 H, 2 x Ph); ν_{max} (solution) 3398 (OH), 2941 (CH). (NMR agrees with Lit.[14])

3-[4-(4,6-Diphenyl-[1,3,2]dioxaborinan-2-yl)-phenyl]-propionic acid **(29)**



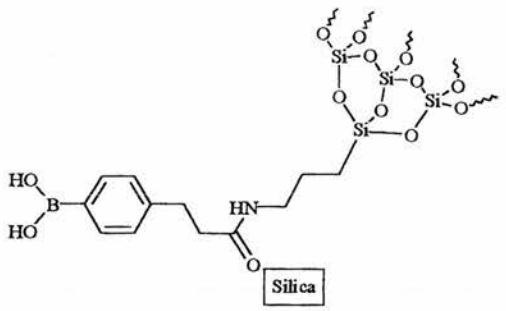
The title compound was prepared using a method developed in house at GlaxoSmithKline for other boronic acids. In toluene (20 ml), 4-(2-carboxyethyl) benzeneboronic acid (1 g, 5.2 mmol), 1,3 diphenylpropane - 1,3 - diol **(29)** (1.18 g, 5.2 mmol) were added together and the mixture refluxed in a Dean-Stark apparatus for 20 hours. The toluene was removed under reduced pressure and the product taken directly to the next step. δ_H ($CDCl_3$) 2.38 (t, *J* 6, 2 H, $CHCH_2$), 2.68 (m, 2 H, CH_2Ph), 2.99 (m, 2 H, $COCH_2$), 5.31 (m, 2 H, 2 x CH), 7.20 – 8.00 (m, 14 H, 3 x Ph); δ_C ($CDCl_3$) 30.7 (CH_2), 35.5 (CH_2), 70.2 (CH_2), 71.1, 73.8 (2 x CH two diastereoisomers), 125.4, 126.5, 127.6, 127.8, 128.4, 128.6, 129.2, 134.6, 142.3, 142.6, 143.3 (3 x Ph two diastereoisomers), 179.1 (CO); ν_{max} (neat) 3225 (OH), 3031 (CO_2H), 2961 (CH), 1703 (CO), 1215 (BO); m/z (ES +ve) 404.2037 ($[M + NH_4]^+$) ($C_{24}H_{23}BO_4 + NH_4$ requires 404.2033).

3-Amidopropyl-(4-(2-carboxyethyl)benzeneboronic acid) functionalised MCM-41 **(30)**



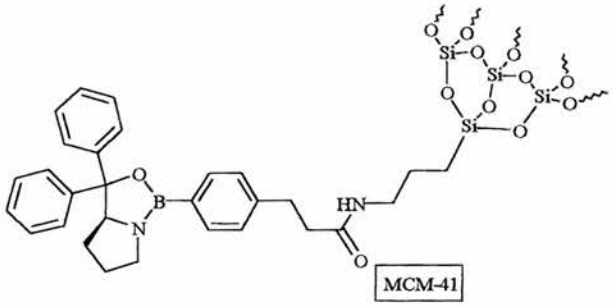
The title compound was prepared using a procedure described by Castro and co-workers.4 Aminopropyl modified MCM-41 **(2)** (0.5 g, loading = 1.8 mmol g^{-1}), 3-[4-(4,6-diphenyl-[1,3,2]dioxaborinan-2-yl)-phenyl]-propionic acid **(29)** (965 mg, 2.5 mmol) and PyBOP (2.6 g, 5 mmol) were added together in acetonitrile (30 ml). To the mixture DIEA (0.87 ml, 5 mmol) was added and the mixture was stirred for 18 hrs. The product was washed well with acetonitrile until TLC showed no compounds washing off the solid in the solvent followed by washing with ether. The product was suspended in 1 N hydrochloric acid: THF (10 ml, 1:3) and stirred for 4 hrs. The solid was filtered and washed with THF and then ether to give the *title compound* **(30)**. The filtrate was washed with sodium bicarbonate and the organic phase was separated and the solvent removed under reduced pressure to give 1,3 diphenyl propan - 1,3 - diol **(28)** (145 mg, 0.635 mmol; equivalent to 1.27 mmol g^{-1} loading of boronic acid on MCM-41); δ_C (MSL) 9.7 ($SiCH_2$), 21.4, ($CH_2CH_2CH_2$), 31.9 (CH_2), 42.7 (CH_2N), 59.5 (CH_2), 128.1 (Ph), 175.9 (CO); δ_B (MSL) 7.39 (B); ν_{max} (KBr disc) 3403 (OH), 2969 (CH_2), 1636 (CO), 1093 (Si-O-Si), 802 (Si-O-Si)

3- Amidopropyl(4-(2-carboxyethyl)benzeneboronic acid) functionalised Silica **(31)**



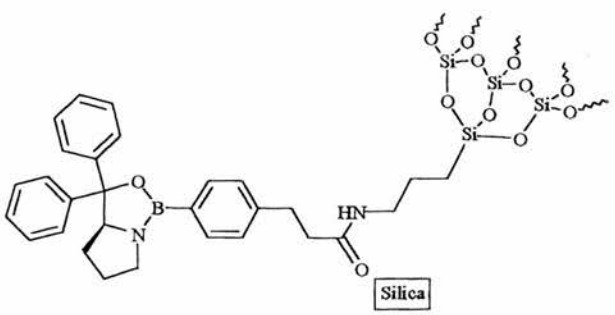
The title compound was prepared using a procedure described by Castro and co-workers.[4] Aminopropyl modified silica (0.5 g, Fluka loading = 1.0 mmol g^{-1}), 3-[4-(4,6-diphenyl-[1,3,2]dioxaborinan-2-yl)-phenyl]-propionic acid **(29)** (480 mg, 1.25 mmol) and PyBOP (1.3 g, 2.5 mmol) were added together in acetonitrile (20 ml). To the mixture DIEA (0.44 ml, 2.5 mmol) was added and the mixture was stirred for 18 hrs. The product was washed well with acetonitrile until TLC showed no by-products in the solvent followed by washing with ether to give the *title compound* **(31)**. The filtrate was washed with sodium bicarbonate and the organic phase separated and the solvent removed under reduced pressure to give 1,3 diphenylpropane 1,3 diol **(28)** (73 mg, 0.321 mmol equivalent to 0.64 mmol g^{-1} loading of boronic acid on MCM-41). δ_C (MSL) 9.8 ($SiCH_2$), 21.6, ($CH_2CH_2CH_2$), 31.7 (CH_2), 42.7 (CH_2N), 64.3 (CH_2), 128.0 (Ph), 176.5 (CO); δ_B (MSL) 8.15 (B); ν_{max} (KBr disc) 3298 (OH), 2960 (CH_2), 1630 (CO), 1081 (Si-O-Si), 802 (Si-O-Si).

Oxazaborolidine prepared from 3- Amidopropyl-(4-(2-carboxyethyl)benzeneboronic acid) functionalised MCM-41 **(30)** *and (S) α,α diphenylprolinol.*



The title compound was prepared using a modified procedure described by Giffels and co-workers.[7] In toluene (25 ml), 3-propylamide-(4-(2-carboxyethyl) benzeneboronic acid) functionalised MCM-41 **(30)** (1 g, loading = 1.27 mmol g^{-1}) and (S)-α,α-diphenylprolinol (964 mg, 3.8 mmol) were added together and the mixture refluxed with a Dean-Stark apparatus for 24 hours. The solid was then filtered and washed with toluene and then ether and dried to give the *title compound* **(32)** as a cream solid; Loading = 0.77 mmol g^{-1} (By weight gain); δ_C (MSL) 10.7 ($SiCH_2$), 23.6, ($CH_2CH_2CH_2$), 31.6 (CH_2), 42.0 (CH_2N), 59.7 (CH_2), 66.0 (CH_2), 78.2 (CH_2), 84.5 (CH_2), 128.2, 145.0 (Ph), 175.4 (CO); δ_B (MSL) – 1.24 (B); ν_{max} (KBr disk) 3405 (OH), 2940 (CH and NH), 1636 (CO) 1081 (Si-O-Si), 802 (Si-O-Si).

Oxazaborolidine prepared from 3-Amidopropyl-(4-(2-carboxyethyl)benzeneboronic acid) functionalised MCM-41 **(33)** *and (S) α,α diphenylprolinol.*



The title compound was prepared using a modified procedure described by Giffels and co-workers.[7] In toluene (25 ml), 3-propylamido-(4-(2-carboxyethyl) benzeneboronic acid) functionalised Silica **(31)** (1 g, loading = 0.64 mmol g^{-1}) and (S)-α,α-diphenylprolinol (488 mg, 1.9 mmol) were added together and the mixture refluxed with a Dean-Stark apparatus for 24 hours. The solid was then filtered and washed with toluene and then ether and dried to give the *title compound* **(33)** as a cream solid; Loading = 0.40 mmol g^{-1} (By weight gain); δ_C (MSL) 10.9 ($SiCH_2$), 22.5, ($CH_2CH_2CH_2$), 31.7 (CH_2), 42.6 (CH_2N), 70.3 (CH_2), 78.0 (CH_2), 127.9, 144.3 (Ph), 174.7 (CO); δ_B (MSL) – 1.24 (B); ν_{max} (KBr disk) 3421 (OH), 2941 (CH and NH), 1652 (CO) 1096 (Si-O-Si), 802 (Si-O-Si).

2.3 References

1 J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt, C. T-W. Chu, D. H, Olson, E. W. Sheppard, S. B. McCullen, J. B. Higgins and J. L. Schlenker, *J. Am. Chem. Soc.*, 1992, **114**, 10834.

2 F. Hunter, Honours Thesis, University of St Andrews, 1998.

3 I. Schön and L. Kisfaludy, *Synthesis*, 1986, 303.

4 D. Le Nguyen, R. Seyer, A. Heitz and B. Castro, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1025.

5 E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551.

6 B. T. Cho and Y. S. Chun, *J. Chem. Soc. Perkin Trans. 1.*, 1990, 3200.

7 G. Giffels, J. Beliczey, M. Felder and U. Kragl, *Tetrahedron: Asymmetry*, 1998, **9**, 691.

8 A. Vogel, *Vogel's Textbook of Practical Organic Chemistry*, Longman, USA, 1978.

9 L. Kisfaludy, M. Löw, O. Nyéki, T. Szirtes, I. Schön, *Liebigs Ann. Chem.*, 1973, **9**,1421.

10 T. Sugawara, K. Kobayashi, S. Okamoto, C. Kitada and M. Fujino, *Chem. Pharm. Bull.*, 1995, **43**, 1272.

11 H. Rehwinkel and W. Steglich, *Synthesis*, 1982, 826.

12 M. Narita, Y. Kojima and S. Isokawa, *Bull. Chem. Soc. Jpn*, 1989, **62**, 1976.

13 M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli and D. Bartoli, *Tetrahedron*, 1988, **44**, 2261.

14 F. Foubelo and A. Gutierrez and M. Yus, *Synthesis*, 1999, 503.

Chapter 3

Epoxidation Reactions of α,β-Unsaturated Ketones.

3.1 Introduction

3.1.1 Uses of Poly-amino Acids in Synthetic Chemistry.

3.1.1.1 Epoxidation of α,β-unsaturated ketones

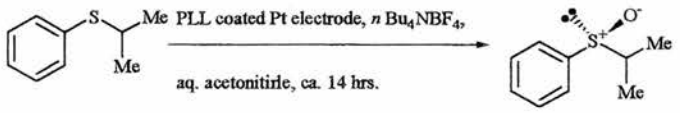
The most widely used application of polyamino acids is the use of poly-L-leucine (PLL) in the epoxidation of α,β-unsaturated ketones.

In 1980 Juliá and co-workers first published a methodology for the asymmetric epoxidation of chalcones in the presence of polyamino acids.[1] The basic procedure involved a triphasic system with the use of basic peroxide, an organic solvent and the insoluble polyamino acid. When the reaction was further studied it was found that a large range of substrates, with the general formula of ArCH=CHCOAr, could be asymmetrically epoxidised in good e.e. and yields.[2] It was found that PLL gave the better results than poly-L-alanine and poly-L-valine give lower conversions and e.e. compared to either PLL or poly-L-alanine.

Juliá and Colonna came to the conclusion that this methodology was limited to chalcone type structures but subsequent work by other groups has widened the number of substrates that can be epoxidised in this manner.[3] This will be discussed in more detail in section 3.1.2.

3.1.1.2 PLL as a Catalyst in the Oxidation of Sulfides.

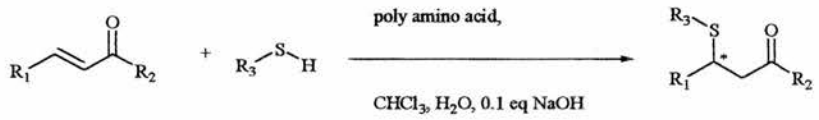
When PLL is coated onto Pt electrodes then this can be used for the oxidation of sulfides in good e.e. For example the oxidation of phenyl *iso*propylsulfide is achieved in 77 % e.e. and in 56 % yield after 14 hrs **(Scheme 20)**.[3]



Scheme 20 – PLL catalysed Oxidation of a Sulfide.[3]

3.1.1.3 Poly Amino Acid Catalysed Michael – Type Reactions.

Various poly amino acids have been used to catalyse the addition of thiols to α,β-unsaturated ketones. The best results were obtained by using thiophenol, changing to "tolylsulfide" (presumably p-thiocresol) has a negative effect on the synthetic process **(Scheme 21)**.[4] The configurations of the products were not reported.



Poly amino acid	Time (hrs)	R_2	R_3	Yield (%)	e.e. (%)
Poly-L-leucine	21	2-naphthyl	Ph	78	25
	22			72	44.5
Poly-L-isoleucine	18			95	24
Poly-L-valine	92			68	10
Poly-L-leucine	20	Ph	(*p*-?) tolyl	96	21
	20	2-naphthyl	Ph	Low	4
Poly-D-leucine	18			64	25[a]
Poly-L-phenylalanine	20			88	16[a]

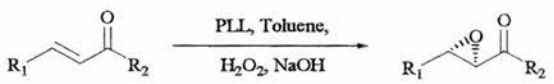
[a] Opposite enantiomer compared to PLL.

Scheme 21 – Poly Amino Acid Catalysed Addition of Thiols to α,β-unsaturated Ketones.[4]

3.1.2 Poly-L-Leucine as an Epoxidation Catalyst.

Poly - L- leucine (PLL), and poly - L - alanine (PLA), are useful heterogeneous epoxidation catalysts.[5] They act as chiral templates directing peroxide (either

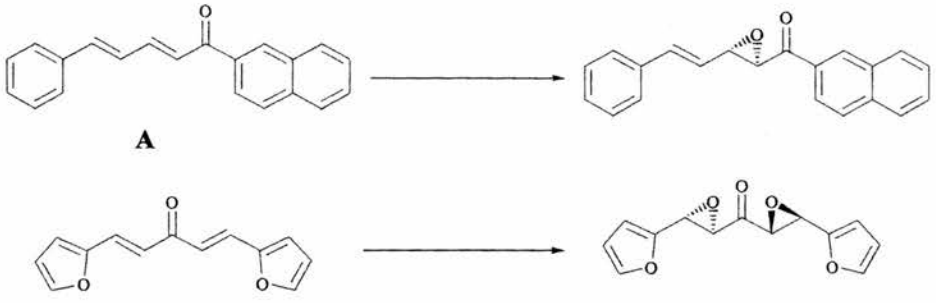
hydrogen peroxide or urea hydrogen peroxide) onto one face of the alkene. Roberts and co-workers[3] have recently reviewed the use of poly-L-leucine as an epoxidation catalyst. The most usual procedure uses insoluble PLL, aqueous hydrogen peroxide and sodium hydroxide with an organic solvent, usually toluene or hexane.[6,7] This procedure gives good yields and high enantiomeric excesses. The PLL polymer is initially 10 - 30 amino acids long, but the basic conditions of the epoxidation reaction gradually break down the polymer. This means the catalyst can only be recycled a few times before activity is lost. The substrate tolerance for this particular epoxidation process is limited, the substrate must have at least one aromatic group to get reasonable yields and good enantioselectivity **(Scheme 22)**.



e.g. R_1 = Ph, 2-furyl, R_2 = Ph, CMe_3

Scheme 22 – Typical PLL Reaction.[3]

It is possible to use milder oxidising agents such as sodium perborate or sodium percarbonate, but the reaction times are longer and there is a reduction in both yield and enantioselectivity. Scheme 20 shows a substrate with one double bond; however this catalytic system is also active for substrates with more than one double bond. Where there is more than one double bond the epoxidation is selective and only the double bond next to the carbonyl reacts **(Scheme 23)**.[3] Therefore, in the presence of PLL, dienone A gives the monoepoxide whereas dienone B gives the bisepoixide.[6]



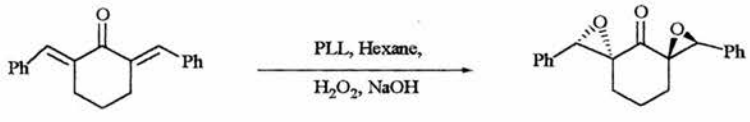
A

B

Dienone	Solvent	Time/ hrs	Yield/ %	e.e./ %
A	Hexane	72	78	> 96
B	CH_2Cl_2	60	60	90

Scheme 23 – PLL catalysed epoxidations of Dienones.[6]

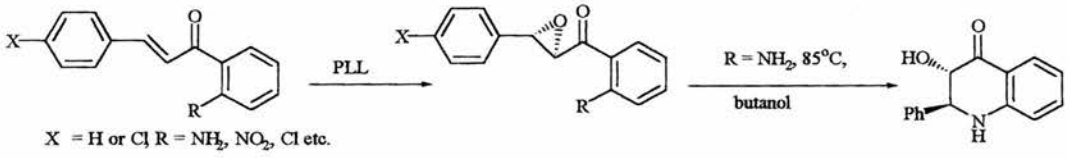
Cyclic ketones have also been investigated but these require the presence of phenyl groups in order to obtain high yields and enantiomeric excesses, and to keep the reaction times practical **(Scheme 24)**.



Scheme 24 – Cyclic Substrates for the PLL Reaction. [3,8]

So far, all reactions described that use PLL are triphasic due to the fact that aqueous hydrogen peroxide is used. If urea-hydrogen peroxide is used in the presence of DBU using THF as the solvent, then a biphasic system can be achieved.[9] The PLL catalyst needs to be activated using the triphasic reaction conditions before it can be used in the biphasic reaction. The yields are lower than seen for the triphasic system, but the enantioselectivities are still good and typically the e.e. for these reactions are approximately 90%.

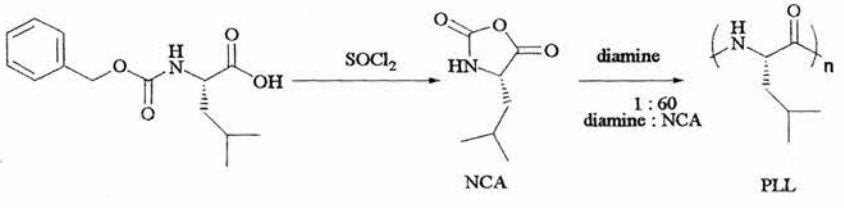
The biphasic method is a useful procedure to prepare bicyclic compounds, such as benzopiperidine **(Scheme 25)**. The PLL reaction is completed as usual to give the epoxide but if there is an internal nucleophile it can cyclise onto the resulting epoxide. In Scheme 23 the internal nucleophile is an amine which at 85°C ring opens the epoxide to give the benzopiperidone.



Scheme 25 – Biphasic PLL Catalytic Reaction.[9]

3.1.3 Mechanistic Insights to the PLL Epoxidation Reaction.

Recently a mechanistic study investigating the important structural features of PLL in epoxidation reactions has been reported.[10] PLL can be synthesised by forming the anhydride, from Z-leucine with thionyl chloride, which will polymerise in the presence of a diamine (ratio 60:1) **(Scheme 26)**.[3,11] The yields of the amino acid N-carboxy anhydrides (NCA) depend on the amino acids used but for leucine are typically around 70 %. In the second step, if 1,3 diaminopropane is used as the diamine, 5 g of the leucine NCA gives approximately 2.8 g of the PLL.[12] This procedure gives a product with a typical molecular weight range of 1500 – 3000 Da.[3]



Scheme 26 – Synthesis of PLL.[11,12]

To investigate the mechanism by which PLL controls the stereochemistry of the epoxidation reaction specific lengths of homo- and hetero-oligomers were prepared.[10] These compounds were attached to polyethylene glycol *via* a hydroxybenzoic acid linker, which was then tethered to a polystyrene resin (PEG-PS) **(Figure 16)**. This was to allow the investigation of which structural properties affected the asymmetric epoxidation of chalcone. Preliminary results suggest that the *C*-terminal region is responsible for the overall orientation of the reactants. The complex is then presented to the *N*-terminal of PLL, which dictates the stereochemistry of the product.[10] Therefore, the 5 residues next to the *N*-terminal are required for the stereocontrol, but the free amine group is not important. However, for the *N*-terminal to give good stereocontrol there must be between 5 and 15 residues adjacent to the *C*-terminus, but the stereochemistry of these latter residues does not affect the overall stereocontrol of the reaction.

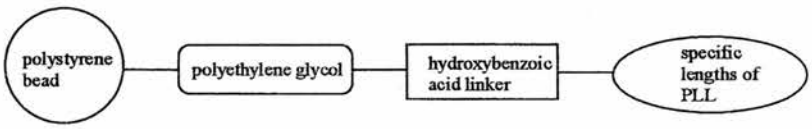
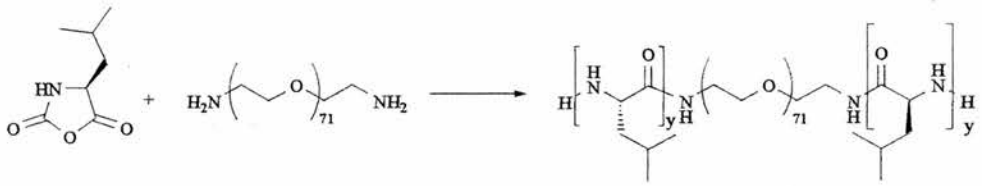


Figure 16 - Model compounds prepared to investigate the mechanism of PLL.[10]

In a recent paper, Roberts and co-workers reported a soluble version of PLL,[13] which was prepared by the reaction of leucine *N*-carboxyanhydride (used in the synthesis of PLL) with *O, O'*-bis (2-aminoethyl) polyethylene glycol instead of the usual diamine initiator **(Scheme 27)**. This produced a polymer which had a oligomer of leucine connected to a specific length of polyethylene glycol (in this example 71 repeat units) which was then connected to another oligomer of leucine. This gave a linear polymer, which is analogous to PLL, except the centre part of the PLL has been replaced with polyethylene glycol.



Catalyst.

Time (h)	Catalyst							
	y = 3.9		y = 7.5		y = 11.6		y = 12.2	
	Yield (%)	e.e. (%)	Yield (%)	e.e. (%)	Yield (%)	e.e. (%)	Yield (%)	e.e. (%)
1	39	97	39	97	36	98	34	97
24	80	98	80	97	63	95	58	96

Scheme 27 - Preparation of A Soluble Analogue of PLL and the Subsequent Epoxidation of Chalcone.[13]

It was found that a minimum of 4 leucines (i.e. y = 4 in scheme 25) on each side of the *O, O'*-bis (2-aminoethyl) polyethylene glycol were required to get good enantioselectivity for the epoxidation of chalcone. The table above shows the results for the biphasic epoxidation of chalcone. Another catalyst with y = 1.8 gave only an e.e. of 5 %. This result cannot be directly compared to the other results as this epoxidation was run under the triphasic conditions. However, it was stated that the other catalysts under these conditions gave better results but no details were given. Increasing the leucine chain length so that y = > 12.2 had no effect on the epoxidation rate or enantioselectivity **(Scheme 27)**. One thing to note is that compared to PLL, the rates of the chalcone epoxidation reaction using these catalysts were much slower.

Ohkata and co-workers investigated an alternative soluble PLL catalyst.[14] This material was prepared by placing one aminoisobutyric acid residue (Aib) in the mid-section of the PLL. With just one Aib in the oligopeptide solubility improves in

organic solvents and promotes α-helix formation. This has been linked to good enantioselectivity but the exact explanation for this is not known. Various lengths of oligopeptides were tested against the epoxidation of chalcone and the results are summarised in Table 5.

Catalyst	Yield of Chalcone oxide %	e.e. of Chalcone oxide %
Boc-L-Leu_4-Aib-L-Leu_4OBzl	50	61
TFA-H-L-Leu_4-Aib-L-Leu_4OBzl	61	68
Boc-L-Leu_4-Aib-L-Leu_6OBzl	60	78
TFA-H-L-Leu_4-Aib-L-Leu_6OBzl	54	73
Boc-L-Leu_6-Aib-L-Leu_4OBzl	89	85
Boc-L-Leu_6-Aib-L-Leu_6OBzl	73	94

Table 5 - Effect of various PLL oligomers containing Aib on the epoxidation of Chalcone.[14]

3.1.4 Aims of This Study.

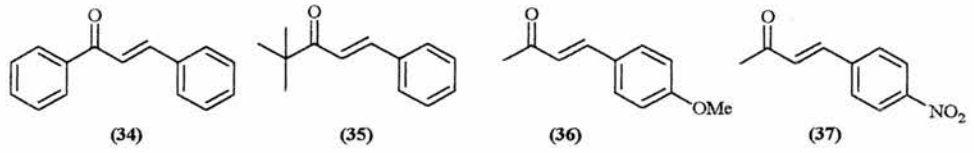
This thesis reports:-

- Effect on the epoxidation of chalcone, of tethering leucine on a solid support.
- Effect of different lengths of oligomers of leucine, tethered to a solid support, on the epoxidation of chalcone.

3.2 Results and Discussion

3.2.1 Substrates for the Epoxidation Reactions.

Four α,β-unsaturated ketones that have previously been used in the poly-L-leucine reactions were chosen for investigation; 1,3-diphenyl-2-propen-1-one **(34)** (chalcone), 5-phenyl-2,2-dimethyl-4-penten-3-one **(35)**, 4-(4-methoxyphenyl)-3-buten-2-one **(36)** and 4-(4-nitrophenyl)-3-buten-2-one **(37)** **(Figure 17)**.[3] Roberts and co-workers have shown that **(34)** and **(35)** are good substrates for the poly-leucine system and **(36)** and **(37)** are poor substrates producing only modest e.e. values **(Table 6)**.[3]



(34) (35) (36) (37)

Figure 17 - Substrates for the Epoxidation Reaction Using PLL.[3]

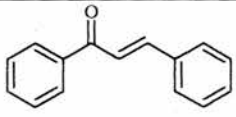
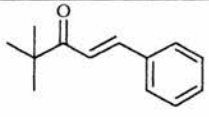
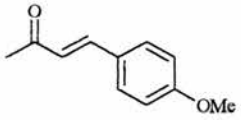
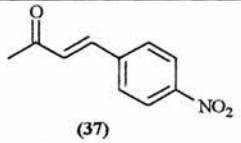
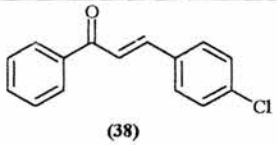
Substrate	Yield %	e.e %	Time (h)	Method
1,3-diphenyl-2-propen-1-one **(34)**	85	94	0.5	A
5-phenyl-2,2-dimethyl-4-penten-3-one **(35)**	76	94	12	A
4-(4-methoxyphenyl) -3-buten-2-one **(36)**	60	62	168	B
4-(4-nitrophenyl)-3-buten-2-one **(37)**	60	60	33	A

Methods: A – Immobilised PLL, urea hydrogen peroxide, DBU, THF; B – PLL, H_2O_2, H_2O, CH_2Cl_2.

Table 6 – Literature Results For Poly-L-Leucine Catalyst in Epoxidation Reactions for Four Different Substrates.[3]

4-Chlorobenzylideneacetophenone (chlorochalcone) **(38)** has also been synthesised but this is not one of the substrates reported by Roberts and co-workers.[3] Chlorochalcone **(38)** was prepared to see the effect of placing a chlorine atom on one

of the aromatic rings. This will alter the overall electronic properties of the molecule and perhaps the asymmetric epoxidation using PLL. All the substrates have been prepared by aldol condensations followed by dehydration to give the α,β-unsaturated ketone. Three methods have been employed to synthesise these five compounds and the table below shows the yields.

Substrate	Method[a]	Time/ hrs	Yield/ %
 (34)	A	3	64
 (35)	B	72	72
 (36)	C	18	64
 (37)	D	24	83
 (38)	A	3	30

[a]Methods will be discussed in the subsequent text.

Table 7 – Yields of Various Aldol Products for the Preparation of Epoxidation Substrates.

Method A involved the ketone and aldehyde being mixed together in aqueous sodium hydroxide solution. As the ketones and aldehydes are not miscible with water, cetyltrimethylammonium bromide (CTAB) was added as a phase transfer

catalyst.[15] In the presence of NaOH and CTAB the aldol and subsequent dehydration took place in one pot.

Method B also used sodium hydroxide but ethanol was added so the system was homogeneous. The reaction proceeded as with method A but the reaction times were much longer because a more hindered ketone was being used.[16]

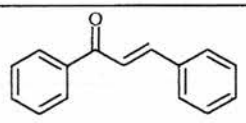
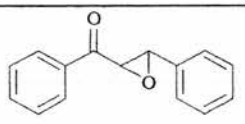
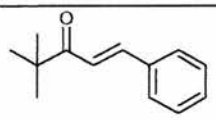
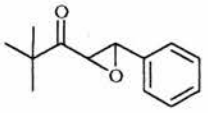
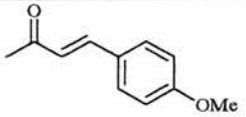
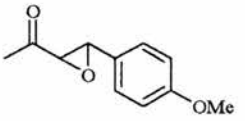
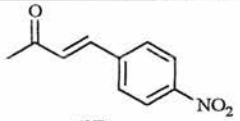
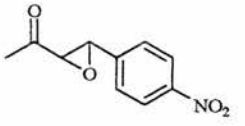
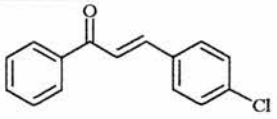
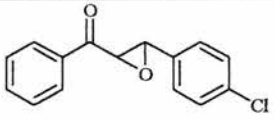
Method C was the same as Method B except that, instead of using ethanol acetone was used as the solvent. Acetone was also one of the reactants for the aldol reaction. Theoretically acetone could react twice, on either side of the carbonyl. Using acetone as the solvent as well as the reactant disfavoured the aldol reaction occurring twice on the same molecule of acetone.[17] This aldol product **(36)** did give problems in the purification steps with the impurities crystallising out with the product after column chromatography.

Method D was used since method A was first tried for the preparation of 4-(4-nitrophenyl)-3-buten-2-one **(37)**, but the conditions were too basic and degradation took place. Method D utilises lower temperature and again acetone as both solvent and substrate.[18] Unlike the other methods the dehydration step did not occur under the same conditions as the aldol reaction. Therefore, the aldol product had to be heated at 65 °C in the presence of 0.5 M sulfuric acid to give the desired product.

3.2.2 Epoxidation Reactions.

Control epoxidation reactions of compounds **34-38** were carried out in the absence of catalyst. In the absence of PLL the reactions were very slow and had to be run

overnight to obtain any product **(Table 8)**.[19] As there was no catalyst all the products were racemic.

Substrate	Epoxide	Yield (%)
 (34)	 (39)	48
 (35)		Could not be isolated but seen in NMR
 (36)		Degradation occurring under reaction conditions.
 (37)		Could not be isolated but seen in NMR
 (38)	 (40)	74

Reaction conditions:- Urea.H_2O_2, DBU, THF, Overnight.

Table 8 – Test Epoxidation Reactions.[19]

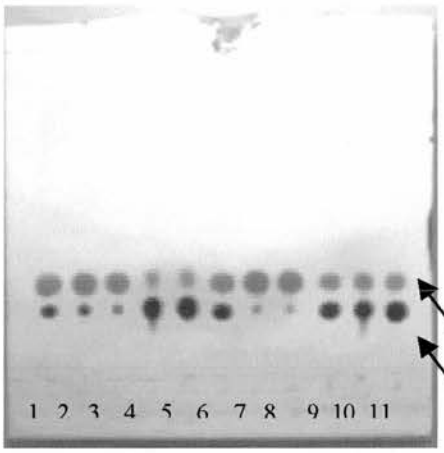
Apart from 4-(4-methoxyphenyl)-3-buten-2-one **(36)** all the aldol products reacted to give the epoxide in the crude reaction mixture seen by NMR. Several attempts were made to produce the epoxide of 4-(4-methoxyphenyl)-3-buten-2-one **(36)** but each time the crude NMR from the reaction showed many products. It was impossible to say whether any of these products was the epoxide and nothing could be separated out of the mixture.

Although crude NMR showed that the epoxidation of 5-phenyl-2, 2-dimethyl-4-penten-3-one **(35)** and 4-(4-nitrophenyl)-3-buten-2-one **(37)** had occurred, neither products could be purified. This was verified by the fact that the protons due to the alkene around 7 ppm had disappeared and peaks around 4 ppm due to the epoxide were present. There was not sufficient epoxide from 4-(4-nitrophenyl)-3-buten-2-one **(37)** to isolate. On the other hand there was sufficient compound produced from the epoxidation of 5-phenyl-2,2-dimethyl-4-penten-3-one **(35)** but any product that was present in the crude mixture degraded on the column and the only solvent system that could be found to obtain crystalline material was ethanol/water. When the NMR of this crystalline material was recorded, no peaks due to the epoxide were present nor was there any in the mother liquor. It was unclear from the NMR what exactly had been formed but it could be possibly the water ring opening the epoxide.

3.2.3 Kinetic Study on Epoxidation Reactions with Novel Molecular Sieves.

3.2.3.1 Method of Analysis.

Roberts and co-workers used chiral HPLC to determine enantiomeric excess and conversion. At the time that this work was undertaken, a suitable HPLC system was not available in house. Therefore, an alternative method was developed to allow several reactions to be modified in parallel. The method involved spotting the reaction mixture on a TLC plate in duplicate as well as standards of starting material and product of known concentration. The plates were then run and were then stained with polymolybdic acid TLC dip, and the intensity of each spot measured using a gel scanner. The actual concentrations in the reaction mixture were then calculated from the intensities observed from the standards spots. A representative example is shown in Figure 17 (See appendix 6.4).



1, 6, 11 = Standard solutions of starting materials and products.

2, 3, 4, 5, 7, 8, 9, 10 = unknown concentrations from reaction mixture.

Chalcone **(34)**

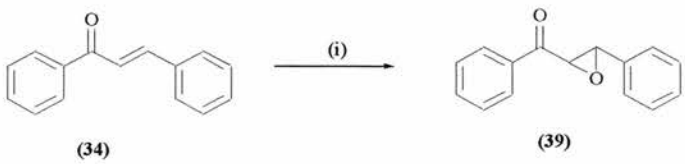
Chalcone oxide **(39)**

Figure 17 –TLC plate used to Determine the Conversion in the Epoxidation of Chalcone in the experiment to determine the effect of leucine tethered to various supported.

Obviously, by the method used here, no information on the enantioselectivity of the reaction can be determined. Hence, the products were purified and the optical rotation measured.

3.2.3.2 Epoxidation Reactions.

The test epoxidation reaction of chalcone **(34)**, in the absence of poly-L-leucine, only gave a 45 % isolated yield after 18 hrs. The literature reports an 80 % yield after 0.5 hrs in the presence of PLL.[3] It is obvious that the PLL does not just impart stereoselectivity to the epoxidation reaction but also a significant rate enhancement. Once these test reactions (in the absence of PLL) had been carried out, investigation of various catalysts was performed using chalcone **(34)** as a substrate **(Scheme 28)**.



(34) (39)

Reagents and conditions: - (i) Urea.H_2O_2, DBU, THF, catalyst, 1.5 hrs.

Scheme 28 – Epoxidation of Chalcone (34).

Table 9 shows the results obtained after 60 min and are based on the conversions calculated from the results obtained from chalcone **(34)**. The conversions calculated from the chalcone **(34)** results had fewer errors compared to the chalcone oxide **(38)** results. This was because at the start of each reaction there was not sufficient chalcone oxide **(39)** present to show up on the TLC. Table 9 quotes the observed conversions divided by the conversions from the background reaction. This gives the ratio of the two conversions and therefore, the amount that the observed reaction is faster than the uncatalysed reaction. (i.e. if the ratio is 2 then the observed reaction is twice that of the uncatalysed reaction, if the ratio is 1 then the rates are the same.)

Catalyst	e.e./ %	Ratio[b]
Commercial PLL	137[a]	1.54
MCM-41 **(1)**	-	1.04
Silica (Fluka)	-	1.02
Aminopropyl functionalised MCM-41-41 **(2)**	-	1.07
Aminopropyl functionalised Silica (Fluka)	-	1.04
L leucinyl amidopropyl functionalised MCM-41 **(8)**	1.0	0.99
Boc L leucinyl amidopropyl functionalised MCM-41 **(9)**	1.2	1.08
Boc L leucinyl L leucinyl L leucinyl amidopropyl functionalised silica **(26)**	Not Available	0.95

[a]Based on literature optical rotation – see text[20]

[b] if the ratio = 2 then the observed reaction is twice that of the uncatalysed reaction See text.

Table 9 – Ratio of conversions for the Epoxidation of Chalcone in the Presence of Various Catalysts.

From the table it can be seen that only the commercially available PLL gave any rate enhancement and e.e. The commercial PLL gave a product **(39)** with an optical rotation of $[\alpha]_D^{25}$ = - 178 (c=1.1, DCM). However, the literature quotes an optical rotation of $[\alpha]_D^{25}$ = - 130 (c=1.1, DCM).[20] This is a little higher than the previously

reported value but it does prove that the PLL has conferred its enantioselectivity on the reaction. This catalyst is not as active as the literature catalysts. The commercial PLL may need activating before it can be used. In the literature, if the PLL is recycled, then before each cycle it must be activated under the triphasic reaction conditions.[3] What effect this has on the PLL is not fully understood.

The other silicates tested all gave negative results both in terms of conversion and enantioselectivity. It was expected that MCM-41 **(1)**, Silica, aminopropyl functionalised MCM-41 **(2)** and aminopropyl functionalised silica would give no rate enhancement as there is no amino acid present to complex with the chalcone and peroxide and bring them together. However none of the amino acid supported catalysts gave any activity at all. This is not so surprising with only one amino acid present as there is probably not sufficient scaffold for the chalcone and peroxide to complex to. However, a tripeptide attached to silica also does not seem to be a scaffold of sufficient size.

3.2.4 Synthesis of potential catalysts based on PAMAM core.

One advantage of the use of silicates is that they are rigid with a defined structure. This can also be a disadvantage if it holds the catalyst in the wrong conformation. To determine if this was going to be a problem, Starburst PAMAM core was also derivatised with leucine. The use of this polymer gives a more flexible core and it was hoped that the peptides tethered to the PAMAM core would interact, producing a better chiral environment to act as the scaffold in the epoxidation of chalcone.

3.2.4.1 Preparation of PAMAM Based Catalysts.

Two different PAMAM cores were used, Generation 1 and generation 0. PAMAM core generation 1 was first used as it has 8 free amino groups that could be derivatised and therefore present a large amount of peptide in the chalcone epoxidation. As will be discussed there were problems in the synthesis and characterisation of this catalyst so PAMAM generation 0 was also used which has 4 free amines. This was hoped to be more straightforward in the preparation and characterisation of the catalyst.

Therefore, PAMAM generation 1 was used to prepare a catalyst made of Boc-tri(L-leucine) **(Figure 18)**. The Boc-tri(L-leucine) was prepared by the same method already discussed in Chapter 2 (Compounds **20** – **25**). Once this catalyst has been prepared by the mixed anhydride coupling method, using *N*-methylmorpholine and *iso*butyl chloroformate, the product was purified by gel filtration on an LH-20 column; however, characterisation proved impossible. NMR was not informative and the product did not "fly" well by MALDI-TOF mass spectrometry. Even under harsh ionisation conditions it was difficult to get any readings on the MALDI-TOF and then there were very small peaks due to compounds with 2, 4, 6, and the full 8 amino groups reacted with the tripeptide.

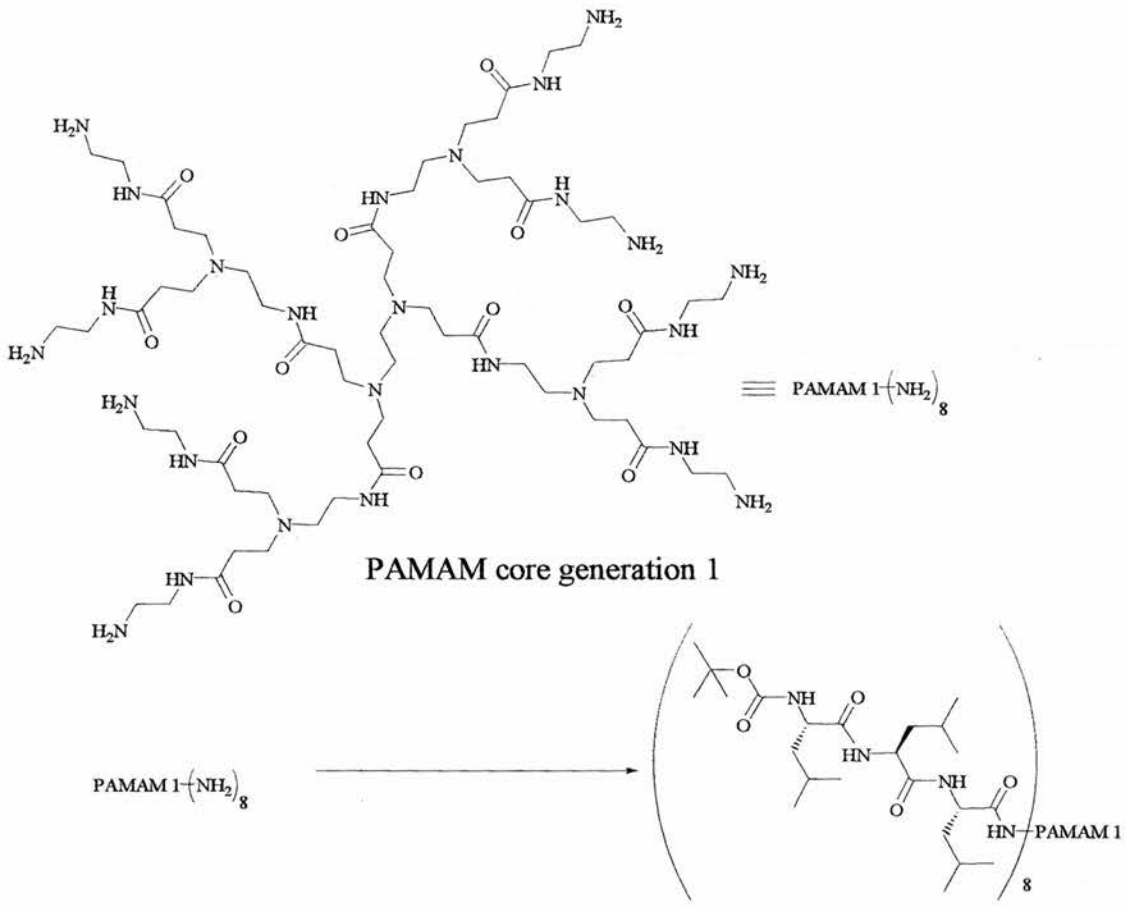
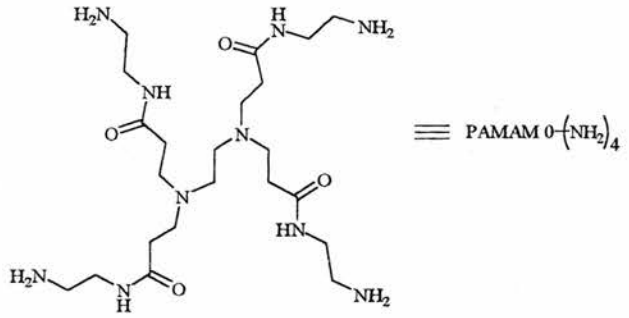


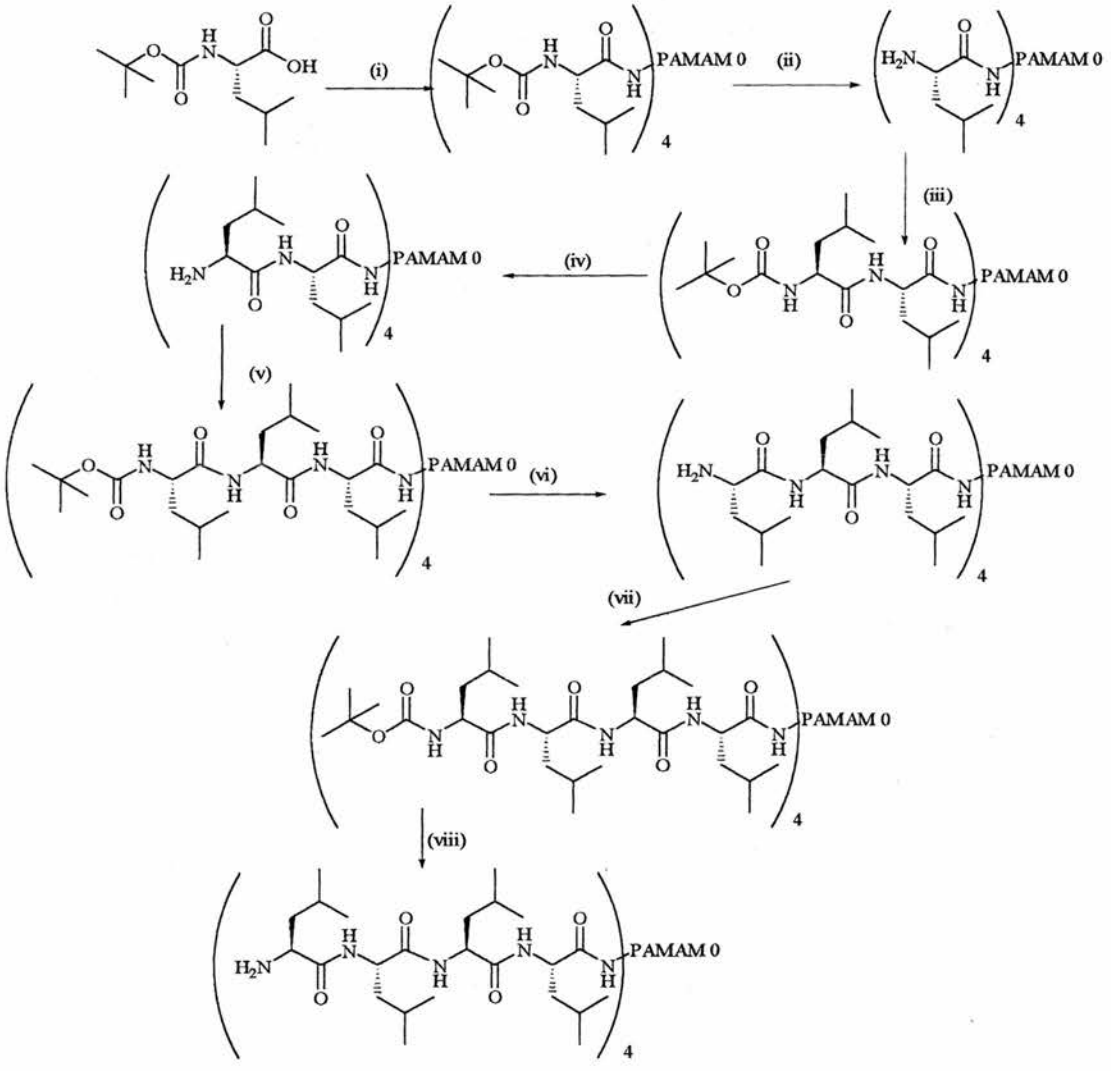
Figure 18 – Attempted preparation of the Potential Chalcone Epoxidation Catalyst Based on PAMAM generation 1 and Boc- L – Leucine.

Although the catalyst in Figure 18 had not been characterised and the exact mixture present in the sample was unknown, it was still tested against the epoxidation of chalcone to see if there was any activity.

The other PAMAM based compound prepared was based on PAMAM generation 0, which has 4 free amines. In this case, the peptide was built up sequentially with the final compound containing tetrapeptides **(Scheme 29)**. A tetrapeptide was prepared because in recent paper by Roberts and co-workers,[13] they showed a minimum of a tetrapeptide was required for an enantioselective catalyst. Again the characterisation proved impossible with both MALDI-TOF and FAB-MS proving ineffective.



PAMAM core generation 0



Reagents and conditions: - (i), (iii), (v), (vii) Boc-L-leucine, PyBOP, DIEA, acetonitrile RT., 3 hrs, (ii), (iv), (vi), (viii) TFA/DCM (1:1), 30 min

Scheme 29 - Synthesis of Boc L Tri Leucine

The only way we have any idea that the couplings were taking place was by the Kaiser test at each stage. After each coupling and deprotection the Kaiser test was

performed to check for free amines. The coupling reactions were worked up when the Kaiser test showed no free amines present and vice versa for the deprotections. Again the material obtained at the end was tested as a potential catalyst in the epoxidation of chalcone.

3.2.4.2 Effect of the PAMAM catalysts in the Epoxidation of Chalcone.

Table 10 shows the results obtained after 60 min and determined in the same way as for the silicate based catalysts. We are not sure exactly what species are in the materials tested as already discussed. The epoxidations were investigated to see if there was any activity; if so, the active species would be sought and investigated further. As can be seen from the table there was not activity so this was not taken any further. There was not sufficient chalcone oxide **(39)** produced to isolate and obtain an optical rotation

Catalyst	Ratio
PAMAM Generation 1 with Boc-L-tri-leucine	1.12
PAMAM Generation 0 with Boc-L-tri-leucine	1.19
PAMAM Generation 0 with L-tri-leucine	1.08

[a]Based on literature optical rotation – see text[20]

Table 10 – Ratio of conversions for the Epoxidation of Chalcone in the Presence of PAMAM based Catalysts.

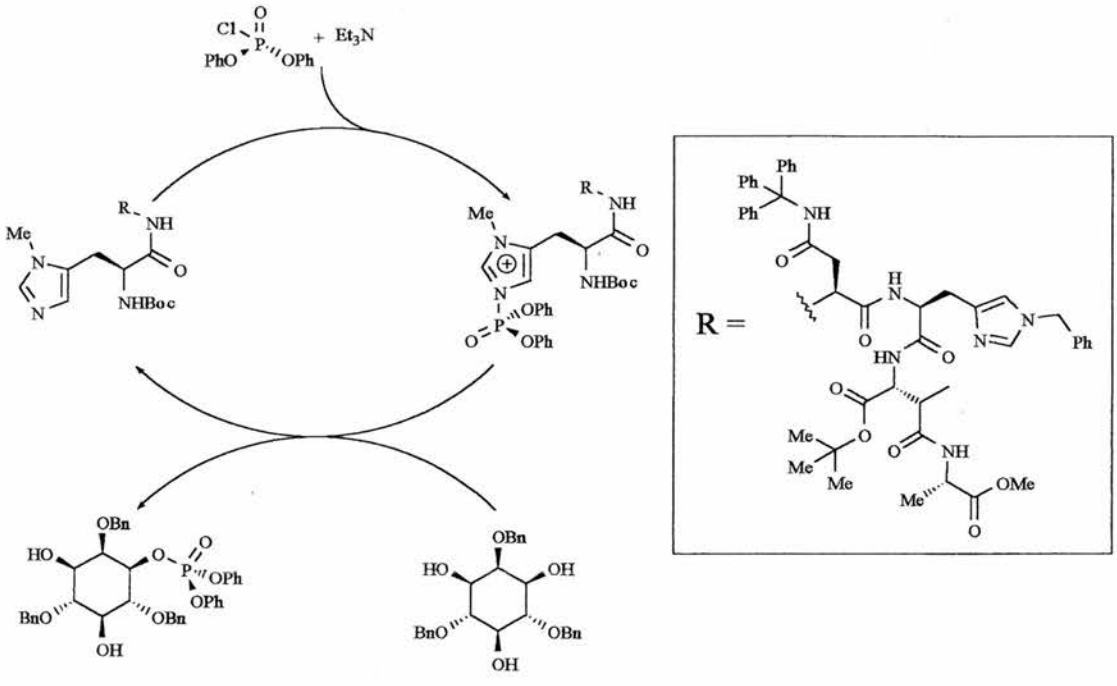
3.2.5 Conclusions to the use of small peptides tethered to silicate supports.

None of the novel catalysts tested has given positive results. This could be due to the insufficient length of the immobilised amino acid residues in the case where only one amino acid is tethered to the support. This investigation shows that the support is very important as regards activity. From the literature it could reasonably be

expected that with the tri- or tetra-peptides some activity should be seen. As we have not seen any activity, the support is also affecting how the chalcone and peroxide complex. The PAMAM based catalysts were tested as it was hoped that with a more flexible core the peptides could come together and act in a similar manner to PLL. These gave negative results but as we could not properly characterise these compounds we cannot say with certainty if these materials, if pure, would be inactive.

3.2.5.1 Literature Example of Small Peptides Catalysing Asymmetric Reactions.

Although this investigation did not produce any potential catalyst, the concept is valid. The use of small peptides to induce enantioselectivity has been reported in a recent paper by Miller and co-workers, who note enantioselective phosphorylation of inositol in greater than 98 % e.e. **(Scheme 30)**.[21]



Scheme 30 - Enantioselective Phosphorylation of inositol using small a peptide.[21]

3.2.6 Future Work.

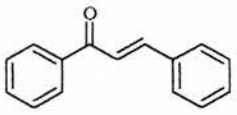
The main area of future work would to look at supporting leucine and oligomers of leucine onto various supports to see the effect both the peptide and support.

3.3 Experimental

As for chapter 2.

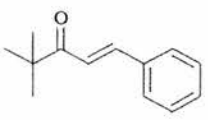
3.3.1 Substrates for the Epoxidation Reactions.

Benzylideneacetophenone (Chalcone) **(34)**



The title compound **(34)** was synthesised by a procedure described by Fringuelli and co-workers.[15] CTAB (344 mg, 0.94 mmol) was added to 0.25 M NaOH (47.2 ml, 11.8 mmol). Benzaldehyde (0.98 ml, 9.4 mmol) and acetophenone (1.19 ml, 10.3 mmol) were added and the mixture was stirred for 3 hrs. The aqueous phase was saturated with NaCl and then the product was extracted with ether. The product was purified by column chromatography (cyclohexane/ toluene 1:4) to give the *title compound* **(34)** (1.28 g, 64 %); m.p. 55 - 56 °C (hexane/ ether), (lit.,[22] 57); δ_H ($CDCl_3$) 7.26-8.05 (12H, m, 2 x CH, 2 x Ph), δ_C ($CDCl_3$) 128.6, 128.7, 128.8, 129.1, 130.7, 132.9 (2 x Ph), 135.1, 138.4 (2 x C quat.), 122.3, 145.0 (2 x CH), 191.4 (CO).

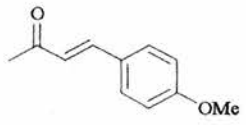
2,2-dimethyl-5-phenyl-4-penten-3-one **(35)**



The title compound **(35)** was synthesised by a procedure described by Hill and co-workers.[16] Into a mixture of ethanol (21 ml) and water (6 ml), *t*-butyl methyl ketone (30.0 mmol, 3 g) and benzaldehyde (33 mmol, 3.6 g) were added together. 10 % sodium hydroxide solution (3 ml) was then added and the mixture stirred for 3 days. The product was then extracted into ethyl acetate and the solvent removed. The product was purified by column chromatography (Hexane: ethyl acetate, 4:1) to give

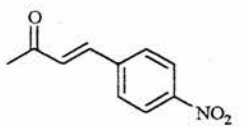
the *title compound* **(35)** (5.7 g, 72 %); m.p. 44 - 46 °C (ethanol/water), (lit.[16] 43); δ_H ($CDCl_3$) 1.23 (9H, s, 3 x CH_3), 7.13 (1H, d, *J* 15.7, CH), 7.38-7.59 (5H, m, Ph), 7.68 (1H, d, *J* 15.7, CH); δ_C ($CDCl_3$) 26.3 (CH_3), 43.2 (quat. C), 128.4, 129.0, 130.3 (Ph), 135.1 (Aromatic C quat.), 120.9, 143.0 (2 x CH), 204.5 (CO).

4-(4-methoxyphenyl)-3-buten-2-one **(36)**



The title compound **(36)** was synthesised by a procedure described by Lawrence and co-workers.[17] In acetone (44.4 ml) 4-methoxybenzaldehyde (2.67 ml, 22.2 mmol) and 10 % sodium hydroxide solution (44.4 ml) were added. The mixture was left to stand overnight. The product was extracted into DCM and purified by column chromatography (toluene and then toluene: ethyl acetate 5:1) to give the slightly impure *title compound* **(36)**; (2.5 g, 64 %); m.p. 76 - 77 °C (*iso*-propanol), (lit.,[23] 74 - 75); δ_H ($CDCl_3$) 2.35 (3 H, s, Me), 3.83 (3 H, s, OMe), 6.59 (1 H, d, *J* 16, CH), 6.99 (2 H, d, *J* 9, CHPh), 7.48(3 H, m, CH and 2 x CHPh), δ_C ($CDCl_3$) 27.3 (Me), 55.4 (OMe), 114.6, 130.1 (2 x CH), 125.2, 143.4 (Ph), 127.2 (C quat.), 161.8 (C quat.), 198.9 (CO).

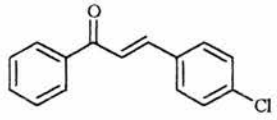
4-(4-nitrophenyl)-3-buten-2-one **(37).**



The title compound **(37)** was synthesised by a procedure reported by Corbett and co-workers.[24] In acetone (12 ml) *p*-nitrobenzaldehyde (1 g, 6.6 mmol) was added and the solution cooled to below 5 °C. 1 % sodium hydroxide solution (1.2 ml) was slowly

added and the mixture stirred for 15 minutes. The solution was acidified by 1 M H_2SO_4 and the acetone was removed under vacuum. The residue was then heated to 65 °C with 0.5 M H_2SO_4 (7 ml). The product was purified by column chromatography (hexane/ ethyl acetate 9:1) to give the *title compound* **(37)** (3.1 g, 83 %); m.p. 96 - 98 °C (ethanol), (lit.[24] 110); δ_H ($CDCl_3$) 2.40 (3H, s, CH_3), 6.80 (1 H, d, *J* 16, CH), 7.53 (1 H, d, *J* 16.5, CH), 7.68 (2H, d, *J* 5, 2 x aromatic CH), 8.25 (2H, d, *J* 5, 2 x aromatic CH); δ_C ($CDCl_3$) 28.0 (CH_3), 111.1, 130.5 (2 x CH), 124.3, 128.9 (4 x aromatic CH), 140.2, 140.9 (2 x C quat.), 177.4 (CO).

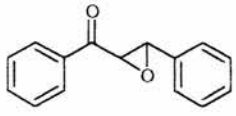
4-Chlorobenzylideneacetophenone (Chlorochalcone) **(38)**



The title compound **(38)** was synthesised by a procedure described by Fringuelli and co-workers.[15] CTAB (34.4 mg, 0.094 mmol) was added to 0.25 M NaOH (4.7 ml, 1.18 mmol). 4-Chlorobenzaldehyde (132 mg, 0.94 mmol) and acetophenone (0.12 ml, 1.03 mmol) were added and the mixture was stirred for 3 hrs. The product was extracted with ether and the product was purified by column chromatography (hexane/ toluene 1:20) to give the *title compound* **(38)** (68 mg, 30 %); m.p. 101 - 103 °C (hexane/ ether), (lit.,[25] 115); δ_H ($CDCl_3$) 7.26-8.05 (11H, m, 2 x CH, 2 x Ph), δ_C ($CDCl_3$) 128.5, 128.7, 129.2, 129.6, 132.9 (2 x Ph), 133.4, 136.4, 138.0 (3 x C quat.), 122.4, 143.3 (2 x CH), 190.2 (CO). NMR agrees with Lit.[26]

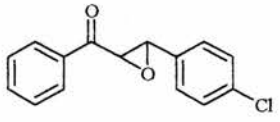
3.3.2 Epoxidation Reactions.

1,3-diphenyl-2,3-epoxy-1-propanone (Chalcone oxide) **(39)**



The title compound **(39)** was synthesised by a procedure described by Roberts and co-workers.[3] In dry THF (1.6 ml) chalcone **(34)** (100 mg, 0.48 mmol), urea hydrogen peroxide (54.2 mg, 0.58 mmol) and DBU (86 µl, 0.58 mmol) were added together and the mixture was stirred overnight. The solvent was removed under vacuum and the product was purified by column chromatography (hexane/ ethyl acetate 12:1) to give the *title compound* **(39)** (48 mg, 48 %); m.p. 90 - 92 °C (hexane/ ether), (lit.,[27] 96 - 97); δ_H ($CDCl_3$) 4.06 (1H, d, *J* 1.72, CH), 4.24 (1H, d, *J* 2, CH), 7.26-8.02 (10H, m, 2 x Ph); δ_C ($CDCl_3$) 59.4, 61.1 (2 x CH), 125.9, 128.5, 128.9, 129.0, 129.2 (2 x Ph), 135.6, 135.6 (2 x C quat.), 193.3 (CO).

3-(4-chlorophenyl)-1,2-epoxy-1-phenyl propan-1-one (Chlorochalcone oxide) **(40)**



The title compound **(40)** was synthesised by a procedure described by Roberts and co-workers.[3] In dry THF (1.5 ml) chlorochalcone **(38)** (50 mg, 0.21 mmol), urea hydrogen peroxide (33 mg, 0.35 mmol) and DBU (52 µl, 0.35 mmol) were added together and the mixture was stirred overnight. The solvent was removed under vacuum and the product was purified by column chromatography (hexane/ ethyl acetate 2:1) to give the *title compound* **(40)** (40 mg, 74 %); m.p. 77 - 78 °C (ethanol), (lit.,[28] 79 - 80); δ_H ($CDCl_3$) 4.08 (1 H, d, *J* 2, CH), 4.30 (1 H, d, *J* 2, CH), 7.36-8.03 (9 H, m, 2 x Ph); δ_C ($CDCl_3$) 58.7, 61.0 (2 x CH), 127.3, 128.5, 129.1, 129.2, 129.4 (2 x Ph), 134.2, 135.1, 135.5 (3 x C quat.), 193.0 (CO).

3.3.2.1 General Procedure for Test Epoxidation Reactions with PLL Catalysts.

In THF (1 ml) chalcone **(34)** (50 mg 0.24 mmol) and PLL (100 mg) were added together and stirred. Finally, urea hydrogen peroxide (27 mg, 0.28 mmol) and DBU (43 μl, 0.28 mmol) were added and the mixture stirred. The reaction was followed by TLC.

3.3.2.2 General Procedure for Test Epoxidation Reactions with Novel Catalysts.

In THF (1 ml) chalcone **(34)** (50 mg 0.24 mmol) and the catalyst (25 mg) were added together and stirred. Finally, urea hydrogen peroxide (27 mg, 0.28 mmol) and DBU (43 μl, 0.28 mmol) were added and the mixture stirred. The reaction is followed as for the PLL reaction. The reaction was followed by TLC.

3.3.2.3 General Procedure for Test Epoxidation Reactions with Novel Catalysts Based on PAMAM Core.

In THF (1 ml) chalcone **(34)** (50 mg 0.24 mmol) and the PAMAM based material (100 mg) were added together and stirred. Finally, urea hydrogen peroxide (27 mg, 0.28 mmol) and DBU (43 μl, 0.28 mmol) were added and the mixture stirred. The reaction was followed by TLC.

3.4 References

1 S. Juliá, J. Masana and J. Vega, *Angew Chem., Int. Ed. Engl.*, 1980, **19**, 929.

2 S. Banfi, S. Colonna, H. Molinari, S. Juliá and J. Guixer, *Tetrahedron*, 1984, **40**, 5207.

3 J. V. Allen, S. M. Roberts and N. M. Williamson, *Adv. Biochem. Engin.*, 1998, **63**, 125.

4 M. E. Lasterra-Sánchez and S. M. Roberts, *Curr. Org. Chem.*, 1997, **1**, 187.

5 S. Ebraham and M. Wills, *Tetrahedron: Asymmetry*, 1997, **8**, 3163.

6 M. E. Lasterra-Sánchez, U. Felfer, P. Mayon, S. M. Roberts, S. R. Thornton and C. J. Todd, *J. Chem. Soc., Perkin Trans. 1*, 1996, 343.

7 W. Kroutil, M. E. Lasterra-Sánchez, S. J. Maddrell, P. Mayon, P. Morgan and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2837.

8 W. Kroutil, P. Mayon, M. E. Lasterra-Sánchez, S. J. Maddrell, S. M. Roberts, S. R. Thornton, C. J. Todd and M. Tuter, *Chem. Commun.*, 1996, 845.

9 W. P. Chen, A. L. Egar, M. B. Hursthouse, K. M. A. Malik, J. E. Mattews and S. M. Roberts, *Tetrahedron Lett.*, 1998, **39**, 8495.

10 P. A. Bentley, M. W. Cappi, R. W. Flood, S. M. Roberts and J. A. Smith, *Tetrahedron Lett.*, 1998, **39**, 9297.

11 L. E. Æ. Sluyterman and B. Labruyère, *Rec. Trav. Chim. Pays-Bas*, 1954, **73**, 347.

12 P. A. Bentley, W. Kroutil, J. A. Littlechild and S. M. Roberts, *Chirality*, 1997, **9**, 198.

13 R. W. Flood, T. P. Gellar, S. A Petty, S. M. Roberts, J. Skidmore and M. Vork, *Org. Lett.*, 2001, **3**, 683.

14 R. Takagi, A. Shiraki, T. Manabe, S. Kojima and K. Ohkata, *Chem. Lett.*, 2000, 366.

15 F. Fringuelli, G. Pani, O. Piermatti and F. Pizzo, *Tetrahedron,* 1994, **50**, 11499.

16 G. A. Hill, C. S. Spear and J. S. Lachowicz, *J. Am. Chem. Soc.*, 1923, **45**,1557.

17 S. Ducki, J. A. Hadfield, L. A. Hepworth, N. J. Lawrence, C-Y. Liu and A. T. McGown, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 3091.

18 R. E. Corbett and C. L. Davey, *J. Chem. Soc.*, 1955, 296.

19 P. A. Bentley, S. Bergeron, M. W. Cappi, D. E. Hibbs, M. B. Hursthouse, T. C. Nugent, R. Pulido, S. M. Roberts and L. E. Wu, *Chem. Commun.*, 1997, 739.

20 D. Enders, J. Q. Zhu and L. Kramps, *Liebigs Ann. Recueil,* 1997, 1101.

21 B. R. Sculimbrene and S. J. Miller, *J. Am. Chem. Soc.*, 2001, **123**, 10125.

22 C. V. Kumar, D. Ramaiah, P. K. Das and M. V. George, *J. Org. Chem.*, 1985, **50**, 2818.

23 F. Lowe, *J. Org. Chem.*, 1965, **30**, 3000.

24 R. E. Corbett and C. L. Davey, *J. Chem. Soc.*, 1955, 296.

25 T. Urasaki and Y. Ogata, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1285.

26 K. Wantanbe and A. Imazawa, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 3208.

27 A. Wasserman, *J. Am. Chem. Soc.*, 1955, **77**, 590.

28 Bodform, *Ber.*, 1916, **49**, 2798.

Chapter 4

Ring Cyclisation Reactions.

4.1 Introduction

Due to the importance of chirality, synthetic chemists are always investigating new methods for the introduction of stereogenic centres into compounds. A very useful synthetic method involves ring closure reactions. If these can be performed enantioselectively then this will introduce one or more stereogenic centres. This type of reaction leads into a large variety of compounds with varying ring sizes. One type of ring closure reaction involves an internal nucleophilic attack at an electrophilic centre, such as a hydroxyl group attacking an epoxide. This reaction has been widely used in natural product synthesis.

4.1.1 Use of Epoxy Alcohol Ring Cyclisations in Natural Product Synthesis.

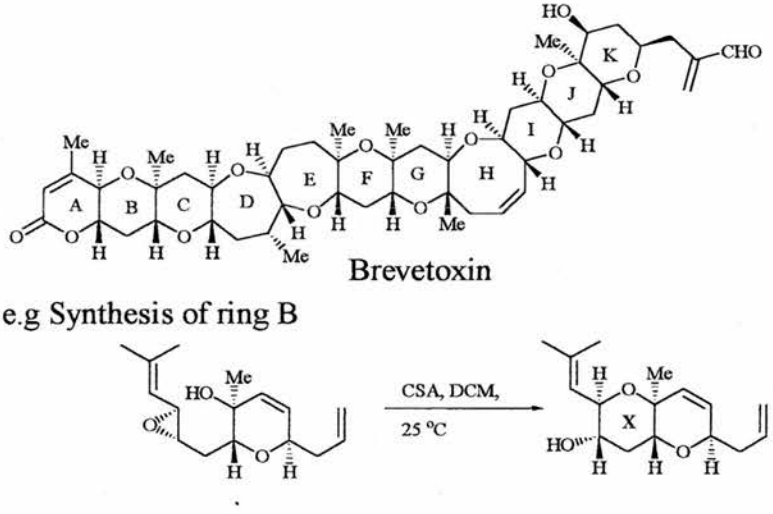
Many natural products contain an oxygen atom within a ring. One method for synthetically preparing these is a ring cyclisation of an epoxy alcohol or epoxy phenol with base or acid. Using this method, different size ring systems can be achieved depending on the conditions and functionality around the epoxide. Some examples of natural product synthesis that use this method are discussed below.

4.1.1.1 Brevetoxins

Brevetoxin B was the first to be discovered in the Brevetoxin class of compounds, and is associated with "Red Tide" catastrophes. Monocellular algae produces this potent lipid-soluble marine neurotoxin and is responsible for the death of fish and other marine life as well as human poisoning.[1,2] Its biological mode of action is to bind to sodium channels forcing them open and causing depolarisation of the cell membrane.[3]

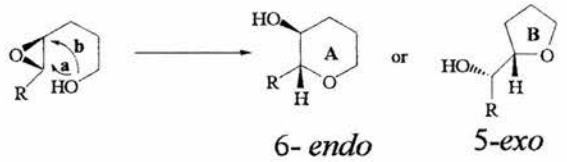
Brevetoxin B has many fused heterocyclic rings, all with stereogenic centres.[4] One efficient method for the synthesis of a tetrahydropyran is the opening of an epoxide by an internal nucleophilic oxygen and has been well studied in the literature.[4,5] The process is highly stereospecific and occurs with inversion of configuration at the epoxide carbon; it can also be very regioselective.[6]

In the synthesis of Brevetoxin B, rings B, F, G and I have been synthesised by this method. For an example, Scheme 31 shows the synthesis of ring B[4]



Scheme 31 – Ring Cyclisation Reaction in the Synthesis of Brevetoxin.[5]

In the above case a 6-*endo* cyclisation was required to form the 6-membered ring. Nicolaou and co-workers studied the effect of the substituent around the epoxide on the size of ring formed **(Scheme 32) (Table 11)**.[4]



Scheme 32 – Possible Ring Sizes From Epoxy Alcohol Cyclisation Reaction.[4]

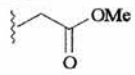
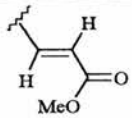
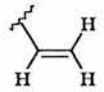
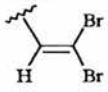
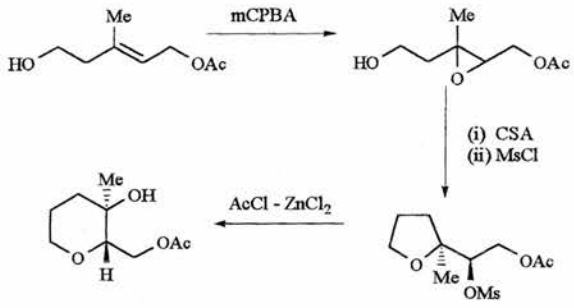
R =	Acidic conditions (Camphorsulphonic acid)		Basic conditions (KOBu^t - Bu^{t}OH)	
	Ratio A:B	**Isolated yield**	**Ratio A:B**	**Isolated yield**
	0:100	94	Ester hydrolysis	
	60:40	96	Ester hydrolysis	
	100:0	95	50:50	85
	100:0	90	95:5	90

Table 11 – Affect of Reaction Condition on Size of Ring Produced in Cyclisation Reaction.[4]

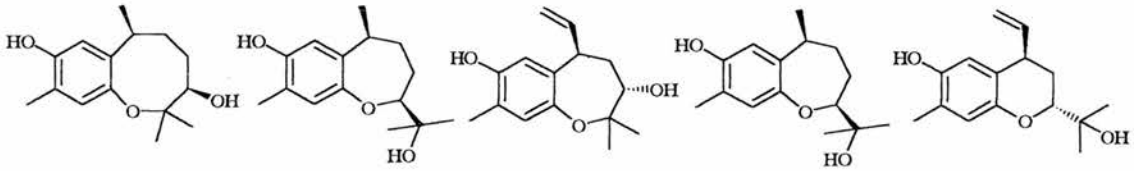
An alternative method utilised in the preparation of Brevetoxin B was to prepare a five membered ring that then rearranged into the required six membered ring.[7] The tetrahydrofuran ring was prepared by an epoxy alcohol intramolecular cyclisation. The epoxy alcohol was prepared from the corresponding alkene with mCPBA. In the presence of CSA, the cyclisation took place and the resulting tetrahydrofuran was then converted to the corresponding pyran ring in the presence of AcCl - $ZnCl_2$ **(Scheme 33)**. The same methodology has been utilised to prepare larger ring sizes.



Scheme 33 - Preparation of Five Membered Rings with Subsequent Rearrangement into Six Membered Rings.[7]

4.1.1.2 (±) – Heliannuol D.

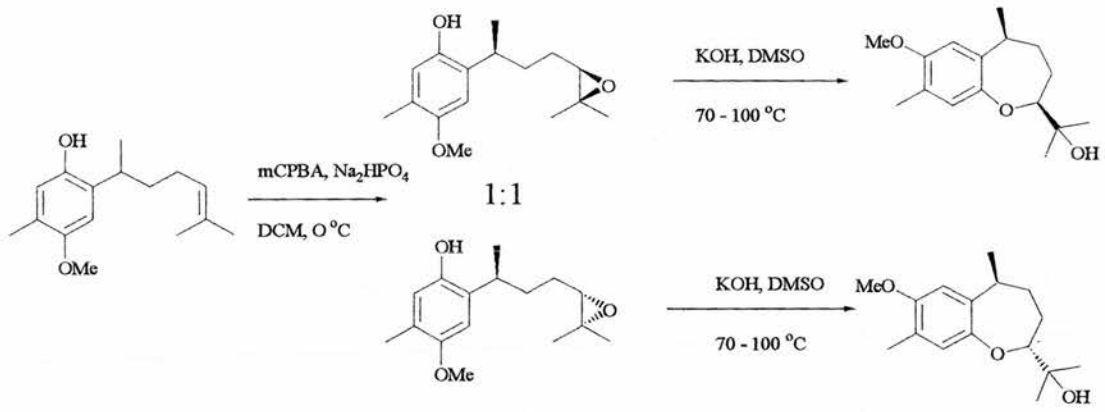
Heliannuols from *Helianthus annus* have natural herbicidal properties against such weeds as Morning glory, velvetleaf, pigweed, jimson weed and wild mustard.[8] Furthermore, they are comprised of previously unknown benzo-fused 6-, 7- and 8-membered cyclic ether structures and are thus challenging synthetic targets **(Figure 19)**.[9]



Heliannuol A Heliannuol B Heliannuol C Heliannuol D Heliannuol E

Figure 19 – Structure of Heliannuols.[9]

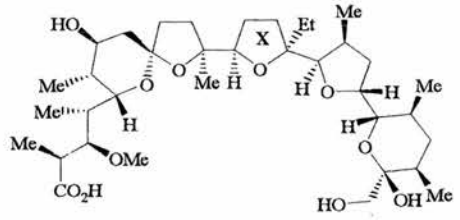
Their synthesis involves the preparation of an epoxide intermediate **(Scheme 34)**. The diastereoisomers were then easily separated by chromatography and then under basic conditions the ring cyclisation was achieved **(Scheme 34)**.[9] The cyclisation conditions are reasonably harsh using potassium hydroxide at 70 °C to 100°C. This may be because a seven membered ring is being formed which is one of the ring sizes that are more difficult to prepare.



Scheme 34 – Ring Cyclisation in the Synthesis of Heliannuols.[9]

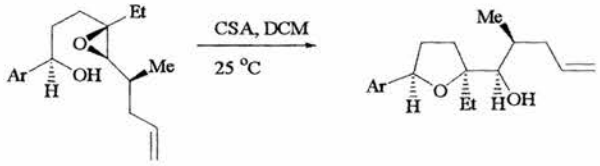
4.1.1.3 Monensin

Monensin exhibits broad spectrum anticoccidial activity and is an additive in cattle feed. It is produced by a strain of *Streptomyces cinnamonensis.*[10] Kishi and co-workers used an epoxy alcohol ring cyclisation reaction to form one of the furan rings in their synthesis of Monensin **(Scheme 35)**[11]



Monensin

Synthesis of Ring X:

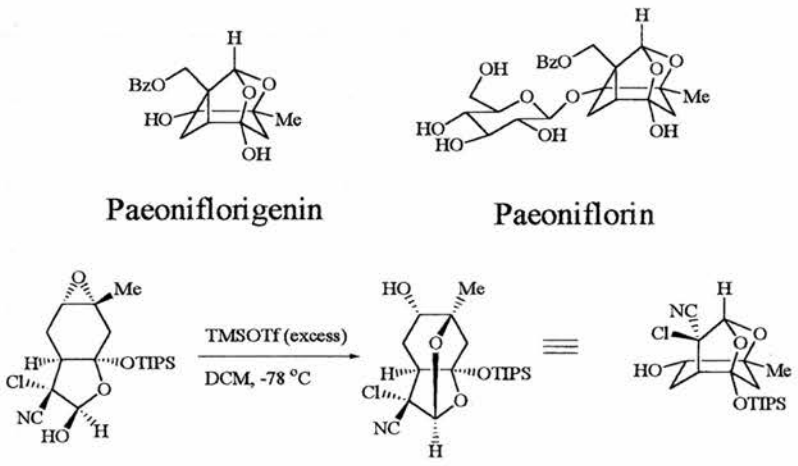


Scheme 35 – Synthesis of One Half of the Tetrahydrofuran Rings in Monensin.[11]

4.1.1.4 Paeoniflorigenin and Paeoniflorin.

Paeoniflorin has played an important part in traditional Chinese medicine as it exhibits sedative, anticoagulant and anti-inflammatory properties.[12] It is extracted

from the root of the Chinese peony *Paeonia lactiflora*.[13] Corey and co-workers first achieved the synthesis of this novel monoterpene in 1993.[14] One of the features of their synthesis is a ring cyclisation of an epoxy alcohol to produce the central core **(Scheme 36)**.



Scheme 36 – Ring Cyclisation of an Epoxy Alcohol in the Synthesis of Paeoniflorin.[14]

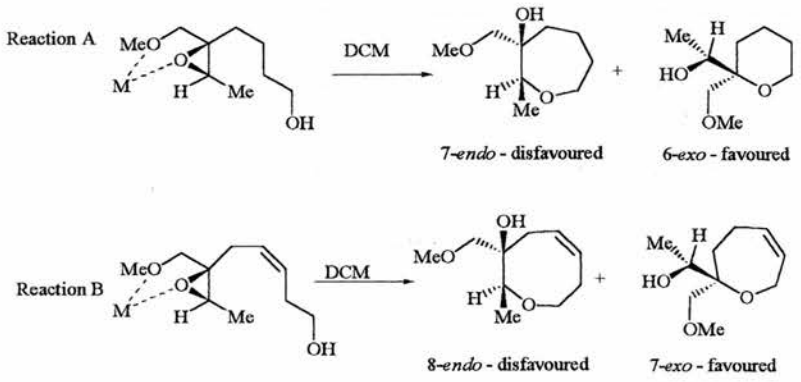
4.1.2 Studies in Controlling Ring Size Formed by Epoxy Alcohol Ring Cyclisations.

It has already been shown with Brevetoxin B, that changing the groups around the epoxide, and the cyclisation conditions, affect the ring size produced **(Table 11)**. The importance of this strategy has led to the investigation in methods for the preparation of specific ring sizes.

4.1.2.1 Use of a Lewis Acid to Control Ring Cyclisation of Epoxy Alcohols.

There have been many reports on 6-endo and 5-exo ring closures. However, there have not been many reported 7-endo and no reported 8-endo cyclisations.[15,16] One strategy is to use a Lewis acid, such as La $(OTf)_3$, to control the cyclisation reaction producing medium sized cyclic ethers. This has been examined for both 7-*endo* and

8-*endo* cyclisations with various Lewis acids.[16] It was found that for both substrates tried, $La(OTf)_3$ gave the disfavoured 7-*endo* and 8-*endo* cyclisation products respectively, whereas the other Lewis acid investigated gave the favoured 6-exo and 7-exo products **(Scheme 37)**.[16]



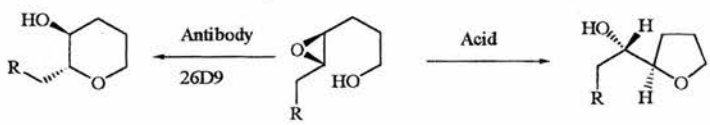
Reaction	Lewis Acid (eq.)	Temp / °C	Time	Yields / %	Ratio *endo* : *exo*
A	CSA (0.1)	20	24 hrs	90	5 :95
	BF_3OEt_2 (1.1)	20	1 hrs	61	3 : 97
	$Zn(OTf)_2$ (1.1)	20	3 hrs	70	21 : 79
	$La(OTf)_3$ (1.1)	20	3 days	73	81 : 19
B	CSA (0.1)	25	11 days	4	44 : 59
	BF_3OEt_2 (1.1)	5	17 hrs	56	22 : 78
	$Zn(OTf)_2$ (1.1)	20	3 days	49	84 : 16
	$La(OTf)_3$ (1.1)	25	6 days	42	96 : 4

Scheme 37 – Effect of Lewis Acid on Disfavoured Ring Closure Reactions.[16]

The success of $La(OTf)_3$ is probably due to its ability to chelate rigidly between the oxygen atom and the strength of the Lewis acidity. The Lewis acidity is strong enough to cause the cyclisation but not too strong so side reactions are kept to a minimum.

4.1.2.2 Control of Ring Cyclisation of Epoxy Alcohols with Peptides.

Since the cyclisation of epoxy alcohols is kinetically controlled, the product depends on the energy barrier of the reaction.[17] A catalyst will lower the energy barrier allowing disfavoured processes to occur. Learner and co-workers had already shown that a catalytic antibody can catalyse a disfavoured epoxy alcohol cyclisation **(Scheme 38)**.[18]



Scheme 38 – Products from Epoxy Alcohol Cyclisation Reactions.[18]

Based on this observation, Chiosis examined peptide libraries to catalyse the ring cyclisation.[17] This was carried out in a combinatorial fashion to gain information on what structural properties of the peptide produced a good catalyst.[17] So that the binding interactions could be studied, a transition state analogue of the disfavoured six membered ring derivative was synthesised. If the peptide binds the transition state analogue tightly, the peptide might be expected to lower the energy of the transition state and therefore the activation energy of the cyclisation. An *N*-oxide was used as the transition state analogue. The cationic nitrogen was a mimic for the carbocation formed in the reaction, and the anionic oxygen a mimic for the ring opening of the epoxide. Since the test peptides were tethered to a solid support, a red dye was attached to the *N*-oxide to facilitate the identification of the active peptides **(Figure 20)**.[17]

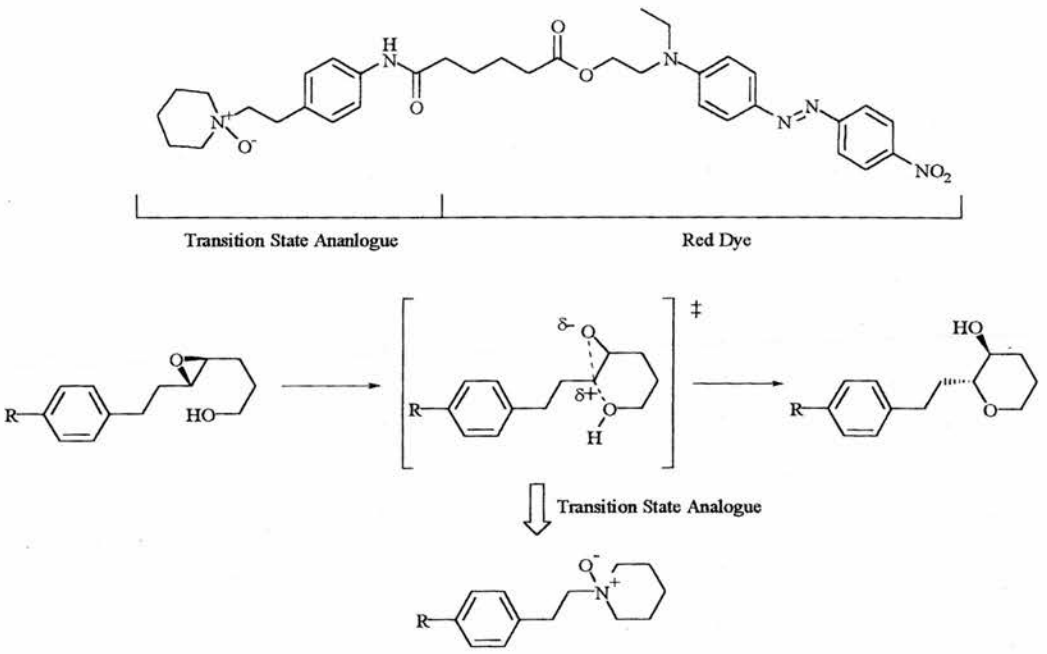
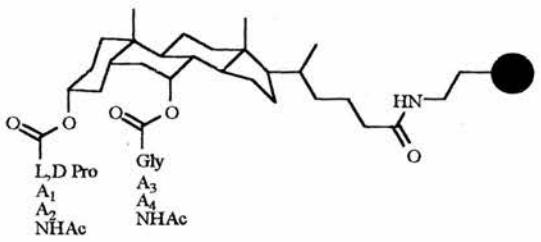


Figure 20 – Transition State Analogue for a Disfavoured Epoxy Alcohol Cyclisation Reaction. [17]

The peptide libraries were randomly chosen and consisted of polystyrene beads with a linker and the peptide. Library **GLPro** consisted of 20,000 members and library **SSY** consisted of 50,000 members **(Figure 21)**.

Library GLPro

Where A_1 A_2 A_3 A_4 are:
L-Ala, L-Pro, L-Leu, L-Phe, L-Pro, L-Ser, L-Thr, L-Lys, L-Glu, L-Asp



Library SSY

Where A_1 A_2 A_3 A_4 are:
Gly, D,L-Ala, D,L-Ser, D, L-Val, D,L-Pro, D,L-Asn, D,L-Gln, D,L-Lys
and CAP are:
Me, Et, *i*-Pr, *t*-But, *i*-Pentyl, *i*-But, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, CF_3, CH_3OCH_2, CH_3COOCH_2, Ph, morpholinyl, NMe_2

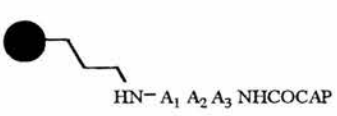


Figure 21 – Test Peptide Libraries for Ring Cyclisation of Epoxy Alcohols. [17]

GLPro and SSY libraries were screened against the transition state analogue in Figure 20. The active beads were identified using the dye attached to the transition state analogue. If the active beads were selected after only one day, the peptides showed a high abundance of Asp and Glu due to unspecific polar interactions of the carboxylates and the *N*-oxide substrate. However, if the beads were left for six days the ratio of amino acids had changed, with a high abundance of Pro and Lys present. In fact, from the library **GLPro**, 70 % of the active peptides had Pro in A_1 position and Lys in the A_3 position. Similar structural properties were seen in the library **SSY (Table 12)**.[17]

A_1	A_2	A_3	CAP
L-Lys	L-Pro	D-Pro	Variable
L-Pro	D-Lys	D-Pro	Variable
D-Pro	D-Lys	L-Pro	Variable
L-Lys	D-Pro	D-Pro	Variable
L-Pro	L-Lys	L-Pro	Variable
L-Ala	L-Pro	D-Lys	Variable
L-Ala	D-Lys	L-Pro	Variable
L-Lys	L-Pro	D-Ala	Variable
L-Lys	L-Ala	L-Pro	Variable
D-Lys	D-Pro	L-Ala	Variable
L-Lys	Variable	L-Pro	Variable
D-Lys	Variable	D-Pro	Variable

Table 12 – Active Sequences from Library SSY to Show Binding to Transition State Analogue.[17]

Molecular modelling studies were carried out on several peptides that had been identified from screening SSY library. These peptides were modelled with the transition state analogue and the epoxide substrate shown in Figure 22.

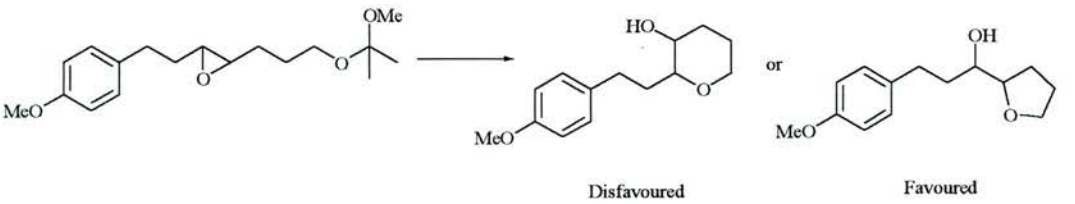


Figure 22 - Epoxide substrate used in the Molecular Modelling Studies and in Subsequent test Reactions.[17]

It was shown that the NH_3^+ group of the Lys was positioned so that it could co-ordinate to the negatively charged oxygen of the *N*- oxide transition state analogue. The conformationally restrictive Pro and internal H-bonds held the Lys in the correct position for *6-endo* epoxide opening **(Figure 23)**.

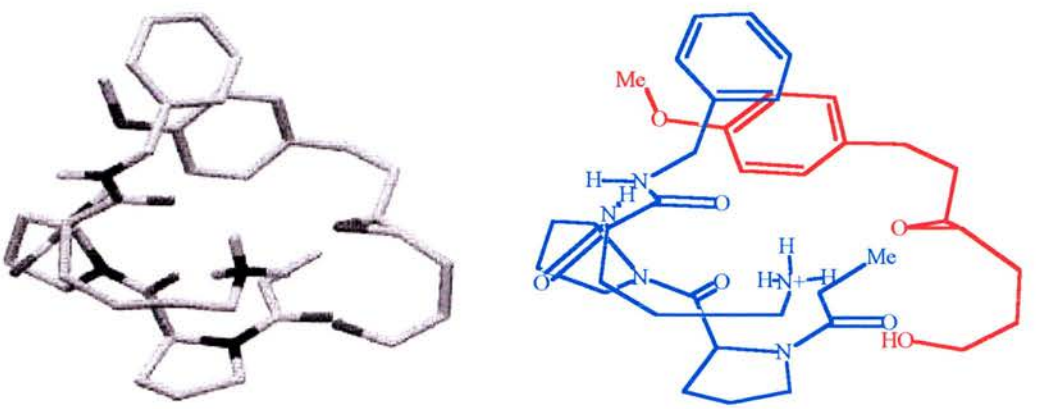
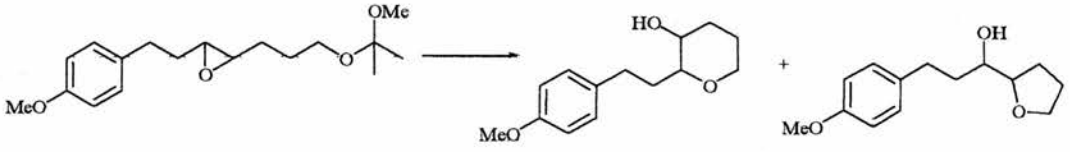


Figure 23 - Molecular Modelling of BnLys-Pro-ProEt.[17]

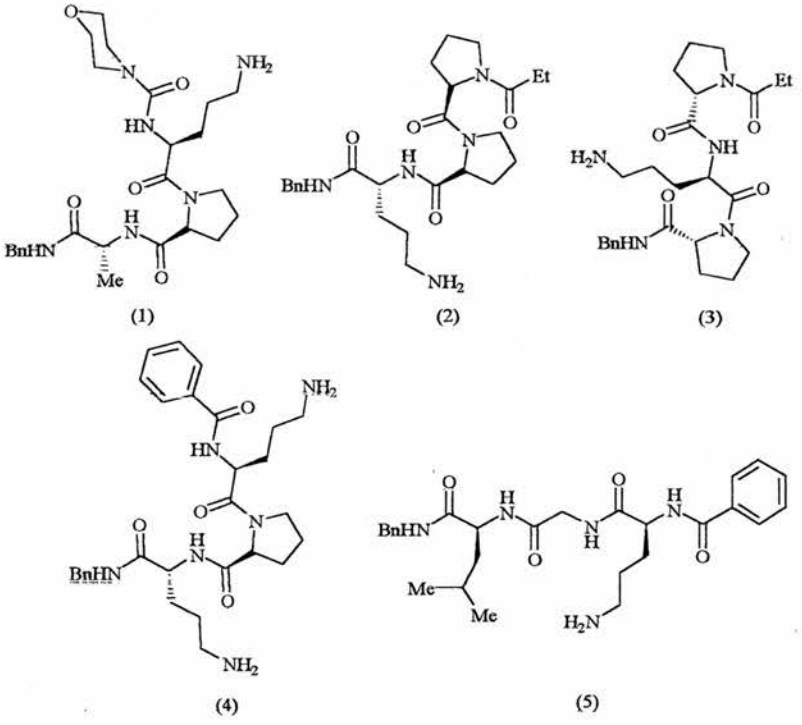
From the molecular modelling results it was suggested that the hydroxyl group, of the substrate, would be favourably positioned for attacking the carbocation formed after the Lys had opened the epoxide. Therefore Chiosis prepared and tested peptides in the solution phase. As none of these peptides had shown strong binding to the transition state analogue, it was expected that these peptides would not be efficient catalysts, and only perform the catalysis to a certain degree. When the cyclisation in the presence of peptides was tried approximately 10 % of the disfavoured 6- *endo*

cyclisation product was formed **(Scheme 39 and Table 13)**. When the epoxide was prepared from the corresponding alkene it was found that it spontaneously cyclised and the epoxide could not be isolated. To prevent this the alcohol had to be protected before the epoxide was prepared. The protecting group was labile enough not to interfere with the peptide catalysed reaction, but stable enough to allow the epoxide to be handled.

Catalysed Cyclisation reaction:



Peptide Catalysts:



Scheme 39 – Epoxide Substrate and Test Peptide Catalysts.[17]

Amount of epoxide used (mM)	Peptide no.	Amount of peptide (mM)			
		2[a]	2[b]	10[b]	20[b]
2	1	11.6	12.7 ± 0.4	10.8	11.2
2	2	13.1	14.0 ± 0.6	13.6	13.6
2	3	13.2	14.3 ± 0.5	12.2	12.1
2	4	1.9	3.6 ± 0.5	NA	NA
2	5	NA	0.9	NA	NA

[a] Solvent = $CHCl_3$:hexane 2:1, [b] Solvent = $CHCl_3$:hexane:THF 1:1:1

Table 13 – Percentage of Disfavoured Cyclisation Product Formed.[17]

These results can now be used to construct a structurally directed library to search for a better catalyst.[17]

4.1.3 Aims of this Study.

- Investigate effect of supported amino acids in the cyclisation of epoxy alcohols.
- Investigate the effect of molecular sieves on iodo cyclisation.

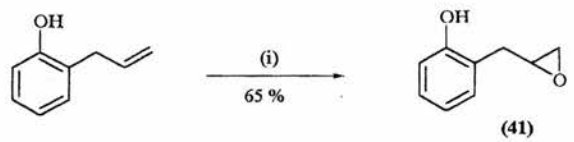
4.2 Results and Discussion.

4.2.1 Synthesis of Epoxy Phenol Substrates.

There are two different features of the cyclisation of epoxy alcohols that can be investigated. The first feature is the enantioselectivity of the cyclisation, namely the stereochemistry of the newly formed stereogenic centre. The other feature is ring size, which depends on which end of the epoxide the alcohol attacks, namely, the regiocontrol of the reaction. These two aspects have been studied separately with two different epoxy alcohols.

4.2.1.1 Preparation of Epoxy Alcohols to Study the Effect of Stereocontrol of the Ring Cyclisation Reaction.

The epoxy phenol that was studied was 2-(2,3-epoxypropyl) phenol **(41)**. This can be easily synthesised from the corresponding alkene with mCPBA **(Scheme 40)**. *o*-Allylphenol is commercially available and the epoxidation reaction was straightforward and proceeded without difficulty.



(41)

Reagents and conditions: - (i) mCPBA, DCM, 0 °C, 1hrs, RT 2hrs.

Scheme 40 – Epoxidation of *o*-Allyl Phenol.

4.2.1.2 Preparation of Epoxy Alcohols to Study the Effect of Molecular Sieves on the Regiocontrol of the Ring Cyclisation Reaction.

An example in the literature of regiocontrol in ring cyclisation was discussed in Scheme 38 and Table 13. In this example using tripeptides as catalysts induced approximately 10 % of the disfavoured 6 membered ring to be formed.[17] It was

therefore decided to prepare the substrate that had been used in the paper by Chiosis[17] and to investigate the effect of molecular sieves on the cyclisation **(Figure 24)**.

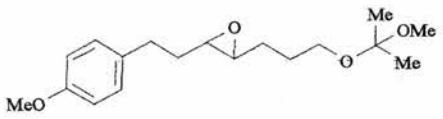


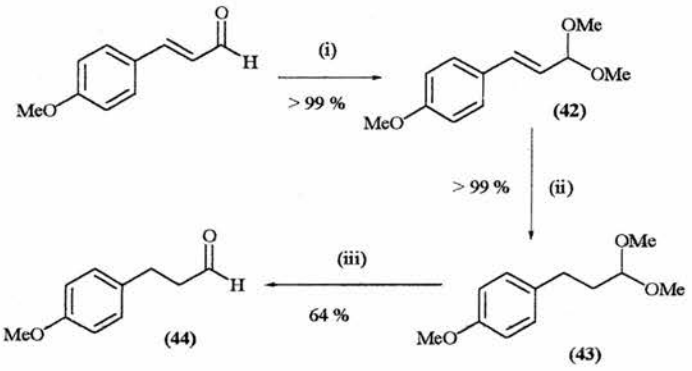
Figure 24 - Literature Substrate For The Investigation Of Regiocontrol In The Ring Cyclisation Reaction.[17]

The first problem that was encountered was the lack of literature experimental. Although two papers had quoted using this substrate there was no experimental data. Chiosis[17] has referenced the original paper from Lerner[18] however as this was an article from Science there were no experimental details. The Lerner paper showed the starting material and the final product with the reagents listed as in Scheme 41. There were no details about the fact that the epoxy alcohol in scheme 41 was found by Chiosis to spontaneously cyclise and therefore the alcohol needed to be protected before the epoxide was formed. Therefore, all the reaction conditions for each step in the synthesis had to be determined.

Reagents and conditions for the synthesis of 1: (a) Montmorillonite K 10, trimethyl orthoformate and hexene; (b) H_2 10% Pd/C, and ethyl acetate; (c) HCl and CH_3CN(aq); (d) 1 M vinyl-magnesium bromide-tetrahydrofuran (THF), -78 °C to 25 °C, 6 hours; (e) triethyl orthoacetate and hexanonic acid, 140 °C, 5 hours; (f) lithium aluminium hydride and THF, -78 °C to 25 °C, 3 hours; and (g) dimethyldioxirane, 15 min.

Scheme 41 – All the Literature details for the Preparation of the Substrate to Study Regiocontrol of epoxy alcohol cyclisations catalysed by peptides.[18]

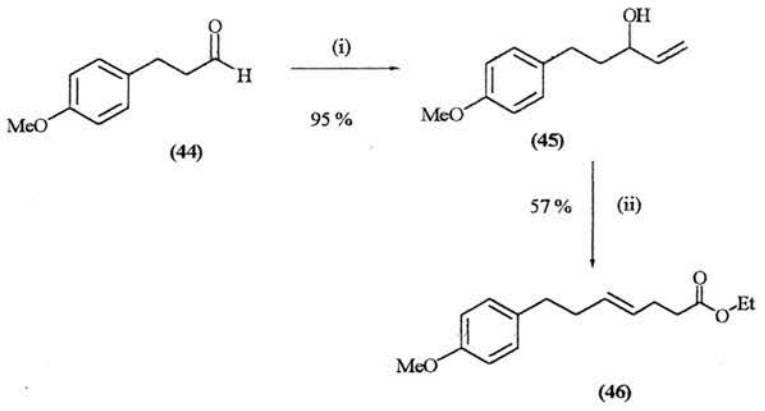
The first step in the synthesis was to protect 4-methoxycinnamaldehyde and then reduce the double bond. **(Scheme 42)**.[18] These two steps were carried out in quantitative yields and no further purification was required. However, it proved difficult to deprotect the aldehyde **(43)** and although various conditions were tried, a yield of approximately 64 % was the best that could be achieved, the remaining 36 % was unreacted starting material.



Reagents and conditions: - (i) Amberlyst 15 (wet), trimethyl orthoformate, hexane, 3 hrs, reflux (ii) H_2, Pd/C, Methanol, RT, overnight (iii) acetonitrile, 2 M hydrochloric acid, ~ pH 2, RT, overnight.

Scheme 42 - First Three Steps in the Synthesis of the Literature Substrate for Test Ring Cyclisation Reactions.[18]

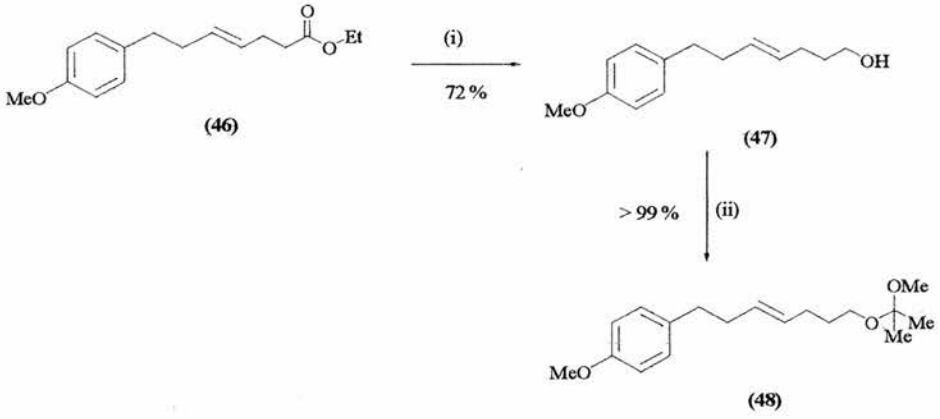
The next step was to increase the chain length by reaction with vinylmagnesium bromide. Subsequent reaction of compound **(45)** with triethyl orthoacetate increased the carbon chain further, as well as producing the double bond from the dehydration of the alcohol **(Scheme 43)**.



Reagents and conditions: - (i) vinylmagnesium bromide, THF, – 10 °C to RT, 3 hr; (ii) triethyl orthoacetate, hexanoic acid, 140 °C, 5 hrs.

Scheme 43 - Reaction of an Aldehyde (44) with a Grignard Reagent and Subsequent Reaction with Triethyl Orthoacetate. [18]

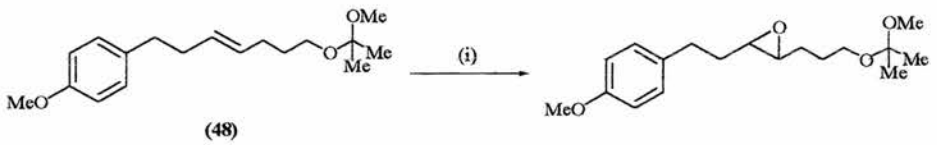
The resulting ester **(46)** was then reduced with lithium aluminium hydride. This completed the synthesis apart from preparing the epoxide from the corresponding double bond. As the literature stated that the epoxide spontaneously cyclised, the alcohol was protected with methoxy propene **(Scheme 44)**.



Reagents and conditions: - (i) $LiAlH_4$, diethyl ether, overnight, RT; (ii) 1-methoxy prop-2-ene, DCM, overnight, RT.

Scheme 44 - Reduction of an Ester (46) and Subsequent Protection of an Alcohol (47). [18]

This is the same protecting group used in the literature and is unstable in acidic and basic conditions. This means the epoxidation of **(48)** had to be under neutral conditions. Dimethyldioxirane is a neutral epoxidation agent, which was used to make the epoxide of this substrate **(Scheme 45)**. The dimethyldioxirane was freshly prepared by the reaction of acetone with potassium monoperoxysulphate (oxone). Unfortunately, the NMR of the crude product from the epoxidation showed many compounds that could not be isolated and accurately assigned. What appeared to have happened, is that even under these neutral reaction conditions some of the protecting group had come off with subsequent cyclisation. By NMR there was still starting material present and perhaps some of the expected epoxide.



(48) Expected product

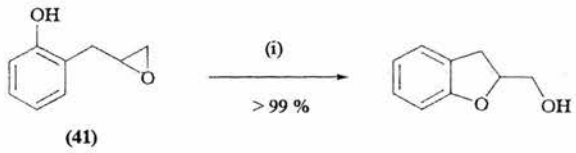
Reagents and conditions: - (i) Dimethyl dioxirane in acetone, DCM, 20 min, RT.

Scheme 45 - Epoxidation with Dimethyl Dioxirane. [18]

Although the epoxidation reaction has caused problems it will still be possible to study the cyclisation of the hydroxy alkene **(47)**.

4.2.2 Enantioselective Ring cyclisation reactions.

In the literature it has been reported found that 2-(2,3-epoxypropyl)phenol **(41)** will undergo spontaneous ring cyclisation under basic conditions **(Scheme 46)**.[19]



(41)

Reagents and conditions: - (i) toluene, base, spontaneous.

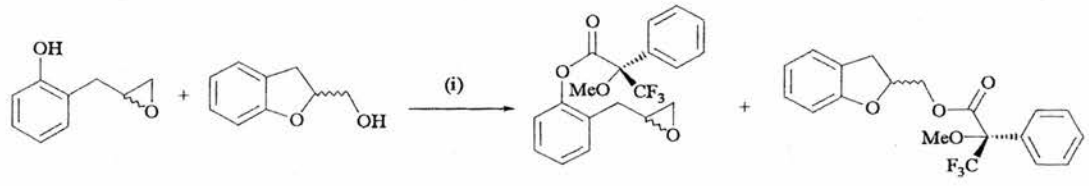
Scheme 46 – Cyclisation of 2-(2,3-Epoxypropyl)Phenol (41).[19]

Consequently, the ring cyclisation was tried with MCM-41 **(1)**, silica (Fluka), aminopropyl functionalised MCM-41 **(2)** and aminopropyl functionalised silica (Fluka). It was found that the silicates alone did not cause the ring cyclisation to occur over a period of 24 hrs. However, both the aminopropyl functionalised MCM-41 **(2)** and aminopropyl functionalised silica (Fluka) produced quantitative yields of the cyclised product (dihydrobenzofuran-2-yl)methanol, within 4 hrs at room temperature.

The next step was to see if an enantioselective cyclisation reaction could be achieved using a chirally modified silicate. If one enantiomer of epoxy alcohol **(41)** cyclised and the other enantiomer did not then this would be kinetic resolution. The maximum yield for this reaction would be 50 %. If this methodology works and goes to completion, in the reaction mixture 50 % of the material would be enantiopure cyclised product and 50 % enantiopure epoxy alcohol **(41)** (the enantiomer that had not cyclised and meaning the reaction had been 100 % selective).

There are many different conditions that might affect the enantioselectivity such as solvent, temperature and the chirally modified silicate. These all need to be tested. So that we could quickly and effectively test for enantioselectivity, the (S)-Mosher's ester of the resulting alcohol product was prepared. The ^{19}F NMR spectrum would then be split to show peaks of the two different diastereoisomers and thus allowe the

e.e. to be determined. However, it was found that the racemic starting material 2-(2,3 epoxypropyl)phenol also reacted with Mosher's acid chloride and these signals in the ^{19}F NMR spectrum also showed the two diastereoisomers of the 2-(2,3 epoxypropyl)phenol **(Scheme 47 and Figure 25)**.



Reagents and conditions: - (i) (S) Mosher's acid chloride, $CDCl_3$, Et_3N, DMAP, 1 hr.

Scheme 47 – Coupling of Mosher's Acid Chloride to Determine e.e.'s.

Unfortunately, as the stereogenic centre of interest is remote to Mosher's reagent and base line separation in the ^{19}F NMR was not obtained. However, there is sufficient separation to use this method qualitatively to find lead catalysts for further optimisation. Eu $(fod)_3$ shift reagent was investigated in an attempt to improve the peak separation. Unfortunately, this did not improve the separations of the peaks and no effect was seen in the ^{19}F NMR of the Mosher's acid derivatives **(Figure 25)**. Investigation of the effect of silicate supported amino acids on ring cyclisation was carried out using ^{19}F NMR to indicate whether or not a racemate is formed.

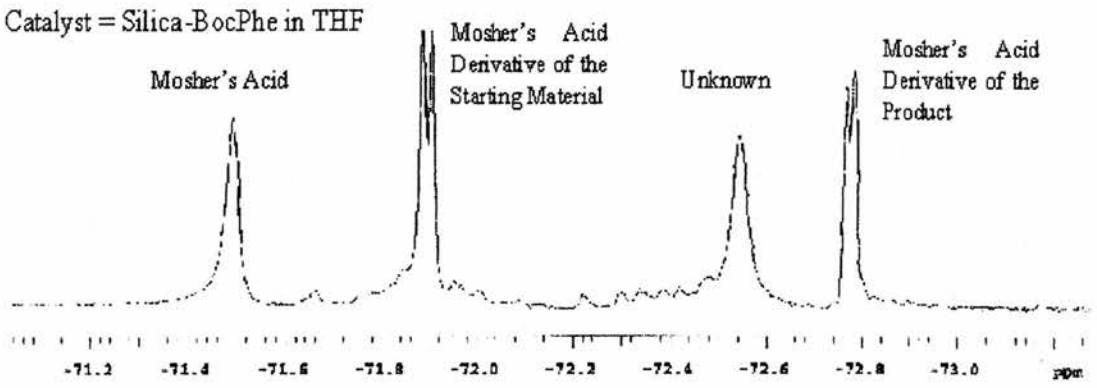
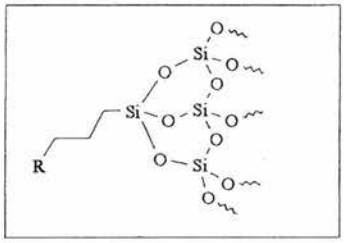


Figure 25 - Example of ^{19}F NMR Spectrum Obtained.

As this is kinetic resolution, the time frame in which the reaction is followed is critical. The analysis must be carried out at 50 % conversion or less because the maximum yield is 50 % and after that if there is any selectivity it will be lost as the other enantiomer of the epoxy alcohol **(41)** will start to cyclise. In all the cases discussed this has been carried out and the time frame used was 4 hours. In this study only one time point was studied because the method of analysis used stopped the reaction. Using another technique, such as chiral HPLC, would allow more time points to be studied and therefore give a better understanding of the reaction.

Ranges of chiral inorganic-organic bases were tested, and these are shown in Figure 26. The cyclisation of 2-(2,3-epoxypropyl)phenol **(41)** was studied varying the solvent, concentration of catalyst and the catalyst itself.



A no catalyst

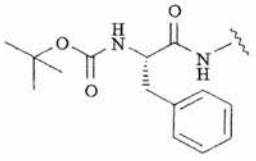
B MCM-41 **(1)**

C Silica (Fluka)

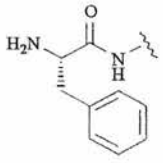
D R = NH_2 (MCM-41) **(2)**

E R = NH_2 (Silica) (Fluka)

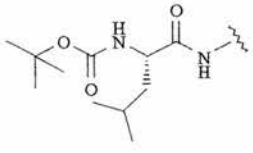
F R = (Silica) **(15)**



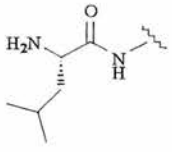
G R = (Silica) **(16)**



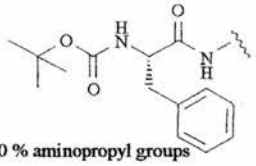
H R = (Silica) **(14)**



I R = (Silica) **(13)**



J R = (Silica) **(16)**



50 % aminopropyl groups

Run	Solvent	Amount of Solvent	Catalyst	Amount of Catalyst	Temp / °C
1	Methanol	0.1 m	0.1 M NaOH	200 µl.	RT
2	Toluene	1 ml	A, B, C, D, E	25 mg	RT
3			E, F, G, H, I, J	25 mg	RT
4				25 mg	40
5		0.5 ml		100 mg	RT
6	DCM	1 ml		25 mg	RT
7		0.5 ml		100 mg	RT
8	THF	0.5 ml		100 mg	RT

All reactions used 15 µl, 25 mg, 0.17 mmol of the *o* – (2,3 – Epoxypropyl)phenol **(41)**

Figure 26 – Various Inorganic-Organic Hybrids Based on Silica Tested as Ring Cyclisation Catalysts of *o* – (2,3 – Epoxypropyl)phenol (41)

Depending on the reaction conditions, products other than the expected were detected by ^{19}F NMR. To try to identify these by-products, components of one of these mixtures was separated by chromatography. However, there appeared to be a large amount of decomposition on the column. Figure 27 shows the ^{19}F NMR spectrum of one such run.

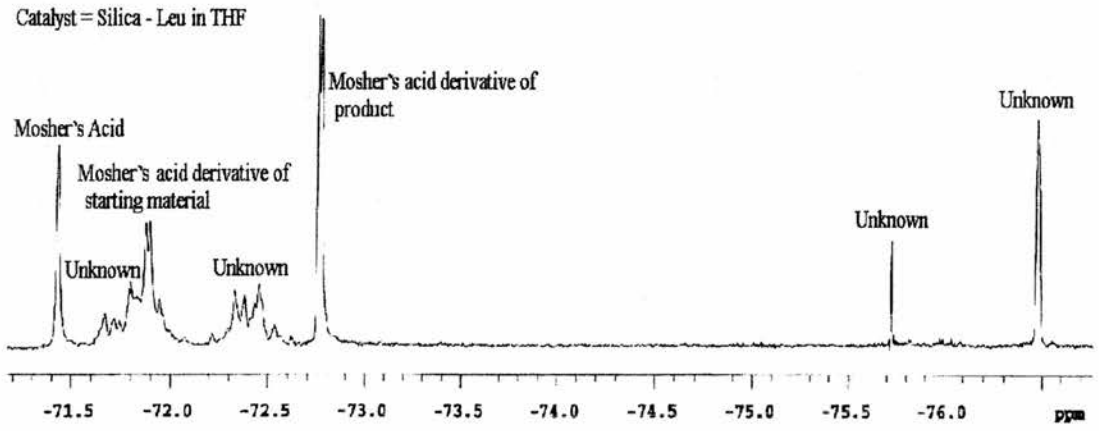
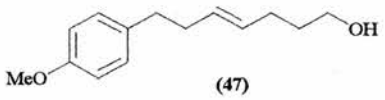


Figure 27 - NMR's of Mosher's Acid Derivatives of the Ring Closure Reactions of *o* – (2,3 – Epoxypropyl)phenol (41).

As long as there was a base present, cyclisation did occur and the extent of the reaction depended on the base. In solution the cyclisation was spontaneous, with aminopropyl functionalised MCM-41 **(2)** it took 4 hours for the reaction to go to completion. With the amino acid functionalised MCM-41 there was approximately 50 % conversion in 4 hours (seen by the ^{19}F NMR of the Mosher's ester). However, the results from the ^{19}F NMR showed that there was no enantioselectivity. Obviously, the *o* - (2,3 – epoxypropyl)phenol **(41)** complexed with the supported catalysts, otherwise, no cyclisation would have been observed. However, this was not sufficient to induce the asymmetry in the reaction.

4.2.3 Regiocontrol in Cyclisation.

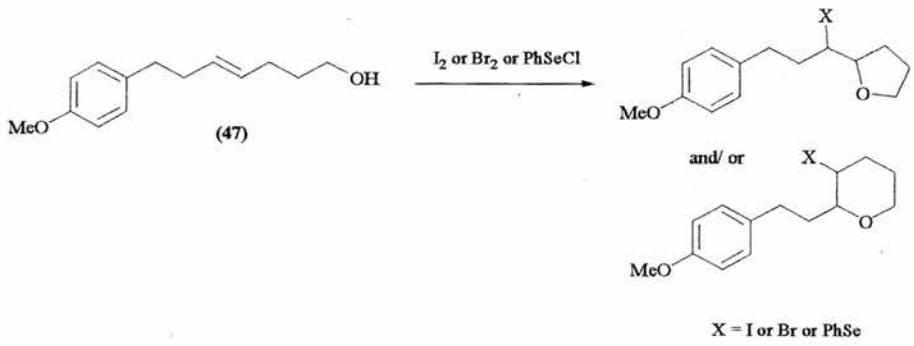
As the epoxidation of alkene **(48)** was proving problematical we decided to look at the cyclisation of the hydroxy alkene **(47)**.



(47)

There are several different methods that can be used to bring about the cyclisation of the substrate above. Some of the methods that can be used are iodo cyclisations,[20,21] bromo cyclisations[22,23] and phenyl selenenyl chloride induced cyclisations.[24,25] Therefore, compound **(47)** was reacted with iodine or bromine or phenyl selenenyl chloride or in the presence of zeolites to see the effect.

The iodo cyclisations and bromo cyclisation were carried out in solution and by supporting the substrate onto silica and achieving the cyclisation in the absence of solvent. The expected products are shown in Scheme 48.



Scheme 48 – Expected Products from the Iodo- or Bromo-cyclisations or Phenyl Selenenyl Chloride induced cyclisations of Compound (47).

Except in the case of iodine with the substrates supported on silica, all the conditions gave a product. No starting material was present as the peaks due to the protons on

the double bond were no longer present in the NMR. However, the product(s) could not be identified, the NMR was very complicated and even moving to 2D did not help. When the substrate was supported on silica and iodine was used hardly any reaction occurred and the NMR showed mainly starting material.

One explanation for the results from the iodo- and bromo- cyclisations was that the products were unstable and degrading. Therefore, phenyl selenenyl chloride was used as this should give a more stable product **(Scheme 48)**. However, when the reaction between phenyl selenenyl chloride and compound **(47)** two spots on the TLC were obtained one being the excess phenyl selenenyl chloride. No starting material was present by TLC and subsequently by NMR. However, after column chromatography, to remove the excess phenyl selenenyl chloride, the product could not be identified by NMR. It was not clear from the NMR as it was complex whether there was one or more products present.

Finally, two acid zeolites were tried, H-ZSM-5 and H-zeolite β. It was hoped in the presence of the zeolite that the alcohol would directly cyclise onto the alkene in compound **(47)**. Compound **(47)** was added to a suspension of H-ZSM-5 in toluene and slowly heated. The reaction was monitored by TLC, but no reaction was apparent, even when it was at reflux. The mixture was refluxed overnight but it was still mainly starting material. However, under the same conditions but with H-Zeolite β instead of H-ZSM-5, no starting material remained after refluxing overnight. However, yet again the product could not be identified from the NMR spectra.

The substrate **(47)** was chosen because the literature quoted that this epoxide cyclised in the presence of small peptides. However, the preparation of the epoxide as well as

compound **(47)** was not well covered in the literature and the synthesis caused problems. Preparation of the epoxide seems to be very sensitive to base and acid and the actual experimental procedure was required to successfully prepare the epoxide, but this was unavailable. Therefore, since compound **(47)** had been prepared, it was decided to use this compound and try various cyclisation techniques. From the results above compound **(47)** does not seem a suitable substrate to study cyclisation reactions as the NMR spectra are too complicated and cannot be interpreted. To try and overcome this problem, COSYs were also obtained but these too did not make sense.

4.2.4 Further Work.

4.2.4.1 Cyclisation of o – (2,3 – Epoxypropyl)phenol (41).

In the presence of amino acid modified silicates *o* – (2,3 – epoxypropyl)phenol **(41)** cyclises but other reactions are also occurring. Further work is required to determine what processes are taking place in the reaction as well as the mechanism of the cyclisation. As already discussed the mechanism is not a simple base-catalysed system. This is because the Boc protected supported amino acids also bring about cyclisation. However, these do not have a free amine to act as a base

None of the silica supported amino acids tested showed any enantioselectivity for the cyclisation of *o* – (2,3 – epoxypropyl)phenol **(41)**. Further increasing the amount of peptide on the support and/ or changing the support could have an effect. Further work on this is required.

4.2.4.2 Cyclisation of Compound (47).

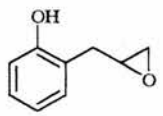
Although the investigation into the cyclisation of compound **(47)** did not give any promising results, there is still scope for further study. The most promising line of investigation would be to prepare the epoxide and test the regiocontrol of the cyclisation reaction. Various peptides both in solution and on a silicate support could be prepared and tested as potential catalysts. As the synthesis of the epoxide proved problematic a new route to this compound would be needed probably involving an alternative protecting group on the alcohol.

4.3 Experimental

As for Chapter 2.

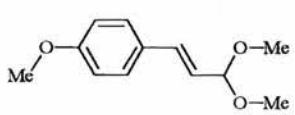
4.3.1 Synthesis of Substrate for Ring Cyclisation Reactions.

o – (2,3 – epoxypropyl)phenol **(41)**



The title compound **(41)** was synthesised by adaptation of the procedure described by Capon and co-workers.[19] In DCM (12 ml) *o* – allyl phenol (7.25 mmol, 0.98 ml) was added and cooled in an ice bath. mCPBA (9.40 mmol, 1.60 g) was then added and the mixture was then stirred for 30 minute in the ice bath and then 1 hr at room temperature. The product was washed with ice cold 10 % sodium hydrogen carbonate solution (2 x 20 ml) and the water (2 x 10 ml). The product was purified by column chromatography (Hexane: EtOAc 9:1) to give the *title compound* **(41)** as a yellow oil. (706 mg, 65 %); δ_H ($CDCl_3$) 2.73 (2 H, m, 1H from CH_2 and 1H from CH_2O), 2.93 (1 H, t, *J* 4.1, 1H from CH_2O), 3.24 (1 H, d, *J* 2.5, 1H from CH_2), 3.29 (1 H, m, CH), 6.84-7.26 (4 H, m, Ph); δ_C ($CDCl_3$) 34.3 (CH_2), 48.0 (CH_2O), 53.3 (CHO), 116.7, 120.7, 128.7, 131.2 (Ar), 123.5 (C quat), 155.5 (COH quat.). NMR agrees with Lit.[19]

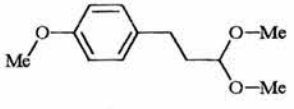
1,1 – Dimethoxy - 3 – (4-methoxyphenyl) – prop – 2 – ene **(42)**



The title compound **(42)** was synthesised by a synthetic scheme described by Lerner.[18] 4-methoxycinnamaldehyde (1.0 g, 6.17 mmol) and Amberlyst 15 (wet) (0.3 g) were added together in hexane (20 ml) under nitrogen. Trimethyl orthoformate

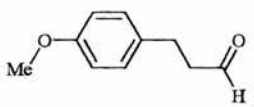
(2.75 ml, 24.68 mmol) was added and the mixture was refluxed for 3 hrs. The mixture was filtered and then the solvent, and excess trimethyl orthoformate, were removed under reduced pressure by co evaporation with toluene to give the *title compound* **(42)** as a dark yellow oil. The product was taken on to the next step of the synthesis without further purification; δ_H ($CDCl_3$) 3.08 (3 H, s, OMe), 3.37 (6 H, s, 2 x OMe), 4.94 (1 H, dd, *J* 1, 4, CH $(OMe)_2$), 6.02 (1 H, dd, *J* 5, 11, CH), 6.64 (1 H, br d, *J* 16, CH), 7.29 (2 H, d, *J* 6, (Ph)CH), 7.36 (2 H, d, *J* 6, (Ph)CH); δ_C ($CDCl_3$) 52.7 (2 x OCH_3), 55.3 (OCH_3), 103.3 (CHO_2), 123.6, 133.2 (2 x CH) 113.8, 128.1, (CH (Ar), 129.0 (C (Ph), C quat.), 159.8 (COMe (Ph) quat.) (NMR consistent with Lit.[26]).

1,1 – Dimethoxy - 3 – (4-methoxyphenyl) – propane **(43)**



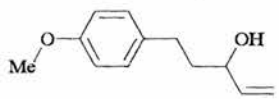
The title compound **(43)** was synthesised by a synthetic scheme described by Lerner.[18] 1,1 – Dimethoxy-3-(4-methoxyphenyl)-prop-2-ene **(42)** (~ 1.2 g, ~ 6 mmol) was added to methanol (20 ml) and to this 10 % Pd/ C (100 mg) was added and the flask was put under an atmosphere of hydrogen and stirred overnight. The mixture was then filtered through Celite and the solvent was removed under reduced pressure to give the *title compound* **(43)** as a dark yellow oil. The product was taken on to the next step of the synthesis without further purification; δ_H ($CDCl_3$) 1.88 (2 H, m, CH_2), 2.64 (2 H, m, CH_2), 3.32 (6 H, s, 2 x OMe), 3.76 (3 H, s, OMe), 4.36 (1 H, t, *J* 6, $CH(OMe)_2$), 6.84 (2 H, d, *J* 6, (Ph)CH), 7.12 (2 H, d, *J* 6, (Ph)CH); δ_C ($CDCl_3$) 29.9, 34.3 (2 x CH_2), 52.7 (2 x OCH_3), 55.2 (OCH_3), 103.8 (CHO_2), 113.9, 129.4 (CH (Ar), 133.8 (C (Ph), C quat.), 158.0 (COMe (Ph) quat.) (NMR consistent with Lit.[27]).

3 - (4-methoxyphenyl) – propanal **(44)**



The title compound **(44)** was synthesised by a synthetic scheme described by Lerner.[18] 1,1 – Dimethoxy - 3 – (4-methoxyphenyl) – propane **(43)** (~ 1.2 g, ~ 6 mmol) was added to acetonitrile (20 ml) followed by 2 N hydrochloric acid dropwise until the solution was ~ pH 2 and then stirred overnight. The product was extracted into DCM and washed with sat. sodium bicarbonate solution (3 x 20 ml) and water (20 ml). The product was purified by column chromatography (hexane : ethyl acetate 7:3) to give the *title compound* **(44)** as a yellow oil; (0.66 g, 64 % over three steps); δ_H ($CDCl_3$) 2.70 (2 H, m, CH_2), 2.89 (2 H, m, CH_2), 3.78 (3 H, s, OMe), 6.82 (2 H, d, *J* 6, (Ph)CH), 7.09 (2 H, d, *J* 6, (Ph)CH), 9.80 (1 H, s, COH); δ_C ($CDCl_3$) 27.2, 45.5 (2 x CH_2), 55.3 (OCH_3), 114.1, 129.6 (CH (Ar)), 132.5 (C (Ph), C quat.), 158.3 (COMe (Ph) quat.), 202.0 (CO), ν_{max} 2936 (CH_2), 1723 (CO). (NMR consistent with Lit.[28])

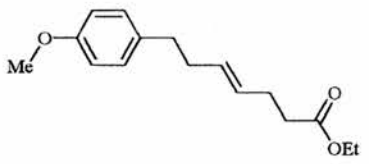
3 – Hydroxy – 5 - (4-methoxyphenyl) – pent – 1 - ene **(45)**



The title compound **(45)** was synthesised by a synthetic scheme described by Lerner.[18] In dry apparatus, vinylmagnesium bromide (3.01 ml of 1.0 M solution in THF) was added to dry THF (2 ml) and cooled to – 10 °C in $CaCl_2$ / ice bath. 3 - (4-methoxyphenyl) – propanal **(44)** (0.33 g, 2.01 mmol in 2.5 ml dry THF) was added dropwise to the mixture not allowing the reaction temperature to go above – 5 °C. The mixture was then stirred for 1 hour at – 10 °C. DCM (10 ml) was added followed by iced water (10 ml) slowly. To this 15 % sulphuric acid (1.5 ml) was added and the

organic phase collected and washed with water until the aqueous phase was no longer acidic. The product was purified by column chromatography (hexane : ethyl acetate 4:1) to give the *title compound* **(45)** as a yellow oil; (0.38 g, 95 %); δ_H ($CDCl_3$) 1.83 (2 H, m, CH_2), 2.66 (2 H, m, CH_2), 3.77 (3 H, s, OMe), 4.10 (1 H, m, CHO), 5.12 (2 H, m, CH), 5.89 (1 H, m, CH), 6.81 (2 H, d, *J* 6, (Ph)CH), 7.11 (2 H, d, *J* 6, (Ph)CH); δ_C ($CDCl_3$) 30.7, 38.8 (2 x CH_2), 55.3 (OCH_3), 72.4 (CHOH), 114.9, 141.3 (2 x CH), 113.9, 129.5 (CH (Ar)), 134.1 (C (Ph), C quat.), 158.0 (COMe (Ph) quat.); ν_{max} 3393 (OH), 2936 (CH_2), 1613 (C=C); m/z 193.1 ($M + H^+$) ($C_{12}H_{16}O_2$ requires 192). (NMR consistent with Lit.[29])

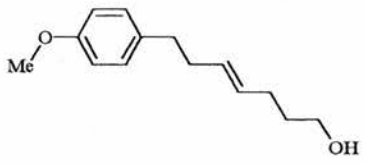
8-(4-Methoxyphenyl) - hept-5-enoic acid ethylester **(46)**



The title compound **(46)** was synthesised by a synthetic scheme described by Lerner.[18] In a Kugelrohr apparatus, 3 – Hydroxy – 5 - (4-methoxyphenyl) – pent – 1 - ene **(45)** (3.8 g, 20 mmol), triethyl orthoacetate (26 ml, 140 mmol) and hexanoic acid (0.15 ml, 1.2 mmol) were added together. The mixture was distilled at 140 °C for 1 hour and then at 150 °C for 2 hrs, to allow ethanol followed by excess triethyl orthoacetate to distil off. The product was purified by column chromatography (hexane : ethyl acetate 3:1) to give the *title compound* **(46)** as a yellow oil; (2.99 g, 57 %); δ_H ($CDCl_3$) 1.25 (3 H, t, *J* 7, CH_3), 2.33 (6 H, m, 3 x CH_2), 2.60 (2 H, t, *J* 7, CH_2Ph), 3.78 (3 H, s, OMe), 4.14 (2 H, q, *J* 7, OCH_2), 5.48 (2 H, m, 2 x CH trans double bond as *J* 11), 6.81 (2 H, d, *J* 7, (Ph)CH), 7.10 (2 H, d, *J* 7, (Ph)CH); δ_C ($CDCl_3$) 14.2 (CH_3), 27.9, 34.3, 34.5, 35.0 (4 x CH_2), 55.2 (OCH_3), 60.2 (CH_2O),

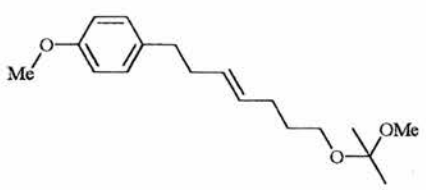
113.8, 129.4 (CH (Ar)), 128.9, 129.4 (2 x CH), 134.2 (C quat.), 157.9 (COMe (Ph) quat.), 173.4 (CO); ν_{max} 2937 (CH_2), 1742 (CO),1614 (C=C).

8-(4-Methoxyphenyl) - hept-5-en-1-ol **(47)**



The title compound **(47)** was synthesised by a synthetic scheme described by Lerner.[18] In dry apparatus, ether (50 ml) and lithium aluminium hydride (1.3 g, 34 mmol) were added together. 8-(4-methoxyphenyl) - hept-5-enoic acid ethyl ester **(46)** (2.99 g, 11 mmol in 25 ml ether) was added slowly so that the ether refluxed gently. The mixture was stirred at room temperature overnight. Water (30 ml) was added slowly. 20 % sulphuric acid was added until all the inorganic salts were in solution. The product was extracted into ether and washed with water. The product was purified by column chromatography (hexane : ethyl acetate 4:1) to give the *title compound* **(47)** as a yellow oil; (1.81 g, 72 %); δ_H ($CDCl_3$) 1.61 (2 H, m, CH_2), 1.75 (1 H, bs, OH), 2.04 (2H. m, CH_2), 2.28 (2 H, m, CH_2), 2.61 (2 H, t, *J* 7, CH_2Ph), 3.60 (2 H, t, *J* 7, CH_2O), 3.78 (3 H, s, OMe), 5.45 (2 H, m, 2 x CH), 6.82 (2 H, d, *J* 6, (Ph)CH), 7.08 (2 H, d, *J* 6, (Ph)CH); δ_C ($CDCl_3$) 28.8, 32.4, 34.6, 35.1 (4 x CH_2), 55.2 (OCH_3), 62.4 (CH_2OH), 113.8, 129.4 (CH (Ar)), 130.3, 130.5 (2 x CH), 134.3 (C quat.), 157.9 (COMe (Ph)); ν_{max} 3389 (OH), 2941 (CH_2),1616 (C=C).

E-1-(2-methoxy-2-methyl-ethoxy)-7-(4-methoxyphenyl)-hept-4-ene **(48)**



The title compound **(48)** was synthesised by a synthetic scheme described by Lerner.[18] In DCM (10 ml), 8-(4-methoxyphenyl)-hept-5-en-1-ol **(47)** (1.4 g, 6.36 mmol) and 2-methoxypropene (25 ml, 31.8 mmol) were added together and stirred overnight. The solvent was removed under reduced pressure to give the *title compound* **(48)** as a yellow oil in quantitative yields; δ_H ($CDCl_3$) 1.34(6 H, s, 2 x CH_3), 1.61 (2 H, m, CH_2), 2.06 (2H. m, CH_2), 2.27 (2 H, m, CH_2), 2.62 (2 H, t, *J* 7, CH_2Ph), 3.20 (3 H, s, OMe), 3.40 (2 H, t, *J* 7, CH_2O), 3.78 (3 H, s, OMe), 5.46 (2 H, m, 2 x CH), 6.82 (2 H, d, *J* 6, (Ph)CH), 7.09 (2 H, d, *J* 6, (Ph)CH); δ_C ($CDCl_3$) 24.4 (CH_3), 29.3, 29.9, 34.7, 35.2 (4 x CH_2), 48.3, 55.2 (2 x OCH_3), 60.1 (CH_2OH), 99.8 (C quat.), 113.8, 129.4 (CH (Ar)), 130.0, 130.5 (2 x CH), 134.3 (C quat.), 157.9 (COMe (Ph)); ν_{max} 2938 (CH_2),1613 (C=C).

4.3.2 General Procedure for the Ring Cyclisation of o – (2,3 – epoxypropyl) phenol (41)

In the solvent (See table below), the epoxide (15 μl) was added and then the base or novel inorganic organic hybrid was added. The test tube was shaken every 30 min and once the TLC shows that the control (reaction containing aminopropyl functionalised silicate) has gone to completion; then the solvent was removed and the residue was dissolved in $CDCl_3$ and placed in a NMR tube. To this triethylamine (5 μl) and DMAP (~ 1 crystal) were added. Finally (S)-Mosher's acid chloride (5 μl) was added and the tube left for 1 hr after which the NMR is recorded.

Run	Solvent	Amount of Solvent	Catalyst[a]	Amount of Catalyst	Temperature / °C
1	Methanol	0.1 m	0.1 M NaOH	200 µl.	RT
2	Toluene	1 ml	A, B, C, D, E	25 mg	RT
3			E, F, G, H, I, J	25 mg	RT
4				25 mg	40
5		0.5 ml		100 mg	RT
6	DCM	1 ml		25 mg	RT
7		0.5 ml		100 mg	RT
8	THF	0.5 ml		100 mg	RT

[a] **A** = no catalyst, **B**= MCM-41, **C** = Silica, **D** = Aminopropyl functionalised MCM-41, **E** = Aminopropyl functionalised silica (Fluka), **F** = Boc-L-Phenylalanine propylamide functionalised Silica, **G** = Boc-L-leucine propylamide functionalised Silica, **H** = L-Phenylalanine propylamide functionalised Silica, **I** = L-leucine propylamide functionalised Silica, **J** = 50 % Derivatised Boc-L-Phenylalanine propylamide functionalised Silica.

Table 15 - Reaction Conditions Studied for the Ring Cyclisation of *o* – (2,3 – Epoxypropyl)phenol (41)

4.4 References

1 Y.-Y. Lin, M. Risk, S. M. Ray, D. Van Engen, J. Clardy, J. Golik, J. C. James and K. Nakanishi, *J. Am. Chem. Soc.*, 1981, **103**, 6773.

2 D. M. Anderson, *Sci. Am.*, 1994, **271**, 62.

3 V. L. Trainer, D. G. Baden and W. A. Catterall, *J. Biol. Chem.*, 1994, **269**, 19904.

4 K. C. Nicolaou, M. E. Duggan, C. K. Hwang and P. K. Somers, *Chem. Commum.*, 1985, 1359.

5 K. C. Nicolaou, C. V. C. Prasad, P. K. Somers and C. K. Hwang, *J. Am. Chem. Soc.*, 1989, **111**, 5330.

6 T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309.

7 T. Nakata, S. Nomura and H. Matsukura, *Tetrahedron Lett.*, 1996, **37**, 213.

8 J. R. Vyvyan and R. E. Looper, *Tetrahedron Lett.*, 2000, **41**, 1151.

9 E. L. Grimm, S. Levac and L. A. Trimble, *Tetrahedron Lett.*, 1994, **35**, 6847.

10 W. M. Stark, *Fermentation Advances*, D. Perlman, Ed., Academic Press: New York, 1969, 517.

11 G. Schmid, T. Fukuama, K. Akasaka and Y. Kishi, *J. Am. Chem. Soc.*, 1979, **101**, 259.

12 W. Tang and G. Eisenbrand *Chinese Drugs of Plant Origin: Chemistry, Pharmacology, and Use in Traditional and Modern Medicine*, Springer-Verlag:Berlin, Heidelberg, 1992, p. 703.

13 N. Aimi, M. Inaba, M. Watanabe and S. Shibata, *Tetrahedron*, 1969, **25**, 1825.

14 E. J. Corey and Y.-J. Wu, *J. Am. Chem. Soc.*, 1993, **115**, 8871.

15 J. E. Baldwin, *Chem. Commun.*, 1976, 734.

16 K. Fujiwara, H. Mishima, A. Amano, T. Tokiwano and A. Murai, *Tetrahedron Lett.*, 1998, **39**, 393.

17 G. Chiosis, *Tetrahedron Lett.*, 2000, **41**, 801.

18 K. D. Janda, C. G. Shevlin and R. A. Lerner, *Science*, 1993, **259**, 490.

19 B. Capon and J. W. Thomson, *J. Chem. Soc. Perkin Trans. 2*, 1977, 917.

20 I. Marek and J. F. Normant, *Tetrahedron Lett.*, 1991, **32**, 5973.

21 T. H. Chan and C. J. Li, *Can. J. Chem.*, 1992, **70**, 2726.

22 A. B. Reitz, S. O. Nortey, B. E. Maryanoff, D. Liotta and R. Monahan, *J. Org. Chem.*, 1987, **52**, 4191.

23 A. K. Saksena, V. M. Girijavallabhan, R. G. Lovey, R. E. Pike, A. K. Ganguly, B. Morgan, A. Zaks, M. S. Puar, and H. Wang, *Tetrahedron Lett.*, 1995, **36**, 1787.

24 S. Konstantinovic, Z. Bugarcic, S. Milosavljevic, G. Schroth and M. L. Mihailo, *Liebigs Ann. Chem.*, 1992, 261.

25 K. C. Nicolaou, R. L. Magolda, W. J. Sipio, W. E. Barnette, Z. Lysenko and M. M. Joullie, *J. Am. Chem. Soc.*, 1980, **102**, 3784.

26 C. Blackburn, R. F. Childs, D. Cremer and J. Gauss, *J. Am. Chem. Soc.*, 1985, **107**, 2442.

27 T. L. Amyes and W. P. Jencks, *J. Am. Chem. Soc.*, 1989, **111**, 7888.

28 G. Parrinello and J. K. Stille, *J. Am. Chem. Soc.*, 1987, **109**, 7122.

29 P. Keiner and R. Bruckner, *Tetrahedron*, 1994, **50**, 13417.

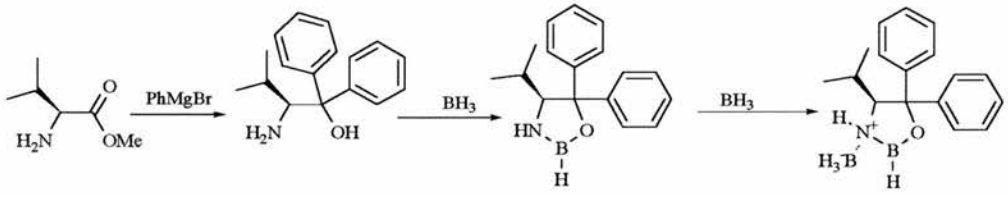
Chapter 5

Asymmetric Reductions Using Oxazaborolidines.

5.1 Introduction

5.1.1 Solution Phase Reductions of Ketones using Oxazaborolidines.

Itsuno and co-workers have studied the enantioselective reduction of ketones using borane complexed to a vicinal amino alcohol.[1,2,3] The amino alcohol derivative from S-leucine provided the most effective oxazaborolidine investigated, for the reduction of various simple ketones. For example, the reduction of acetophenone was achieved in 95% e.e. using this oxazaborolidine **(Scheme 49)**. The oxazaborolidine was prepared by reaction of leucine methyl ester with phenyl magnesium bromide followed by complexation with borane.



Scheme 49 - Itsuno's Reagent for the Conversion of Ketones to Secondary Alcohols.[1]

In 1987, Corey and co-workers reported a new chiral oxazaborolidine for the conversion of ketones to secondary alcohols.[4,5] This oxazaborolidine was derived from proline, which is more hindered than leucine. This oxazaborolidine was prepared in a similar way to Itsuno's reagent. Once this new oxazaborolidine was reacted with borane-THF complex it gave superior results compared to Itsuno's reagent. The typical enantioselectivities obtained from the new oxazaborolidine are shown in Table 14.

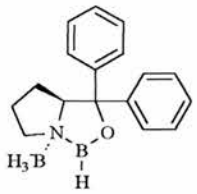
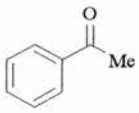
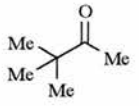
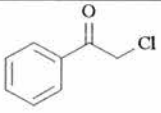
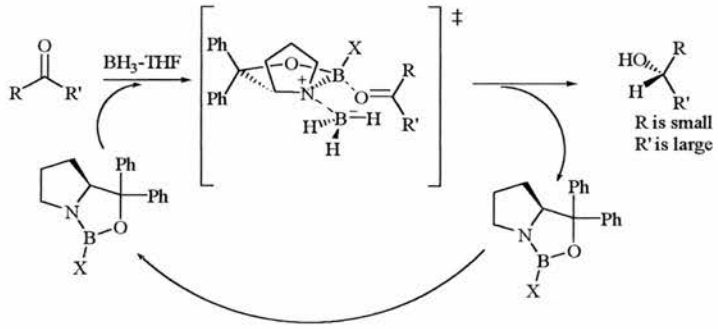
Ketone	Equiv. BH_3	Equiv. of 	e.e. % (Config.)
	2.0	1	97 (R)
	1.0	0.1	97 (R)
	1.2	0.025	95 (R)
	1.2	0.005	80 (R)
	1.2	0.05	86 (R)
	1.0	0.05	88 (R)
	0.6	0.05	90 (R)
	1.0	0.05	81 (R)
	0.6	0.05	88 (R)
	0.6	0.1	92 (R)
	0.6	0.05	97 (S)

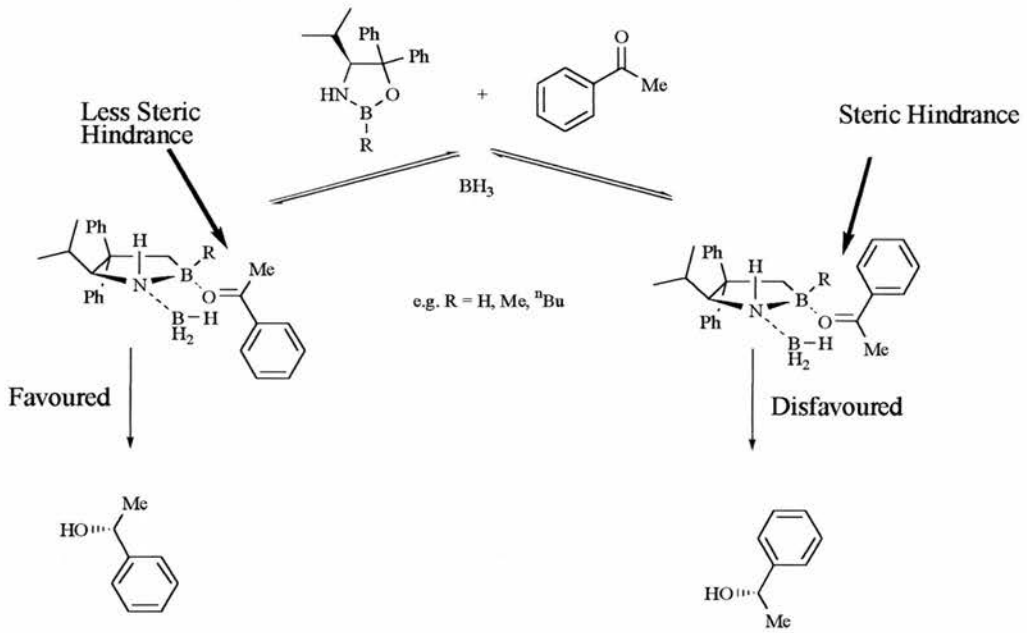
Table 14 - Enantioselective Reduction of Ketones Using the Oxazaborolidine Catalyst in Scheme 41.[5]

The proposed mechanism for the reduction of a ketone is also shown in Scheme 50.[6]



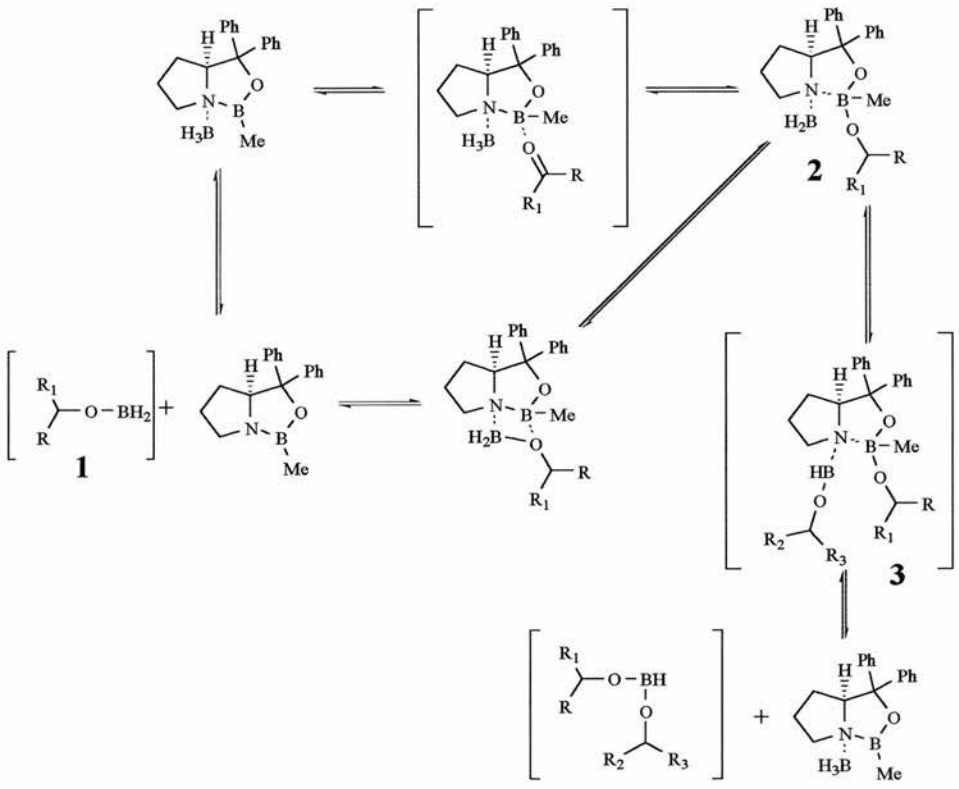
Scheme 50 – Synthesis and Catalytic Mechanism for Oxazaborolidine Reduction of a Ketone.[5]

The enantioselectivity of the reaction can be explained by looking at the transition state of the two different conformations **(Scheme 51)**.[6] The ketone can either co-ordinate with its phenyl group pointing towards the R group on the boron of the catalyst or away from it. The former is disfavoured because there is larger steric hindrance between the R group on the boron and the ketone, compared to the latter.



Scheme 51 - Mechanistic Insight into the Enantioselectivity of the Reduction using Oxazaborolidine.[6]

Douglas and co-workers have conducted a more in depth study.[7] Transient intermediates were detected by *in situ* NMR experiments, and the proposed mechanism is shown below **(Scheme 52)**.



Scheme 52- Proposed Reaction Pathways in the Oxazaborolidine Catalysed Reduction of Ketones.[7]

This mechanism proposes another species **(Scheme 52, Structure 2)** that can reduce ketones but not enantioselectively and therefore reduce the overall enantioselectivity of the reaction. It was proposed if the rate of dissociation of Structure **2 (Scheme 52)** is slow, then structure **2** is an effective reducing agent and can reduce another ketone molecule. However, as the boron on the oxazaborolidine has already one alcohol product complexed to it, then the second ketone cannot complex and the reduction produces the racemic product giving structure 3 **(Scheme 52)**. Nevertheless, it must be remembered this is only proposed from the NMR results, and structures **1** and **3** were not observed in the NMR experiments that were carried out.[7]

The one problem of the oxazaborolidine with hydrogen on boron is that it is very air sensitive. Further development led to a more stable oxazaborolidine with the prolinol

complexed with methylboronic acid rather than a borane-THF adduct **(Figure 28)**.[6] A variety of oxazaborolidines derived from various amino alcohols were investigated, but methyl-CBS-oxazaborolidine is the most widely used and it is commercially available.

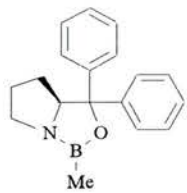


Figure 28 - (S)-Methyl-CBS-Oxazaborolidine - Corey's Reagent.[6]

The crystal structure of this oxazaborolidine complexed with borane has been solved **(Figure 29)**.[8,9]

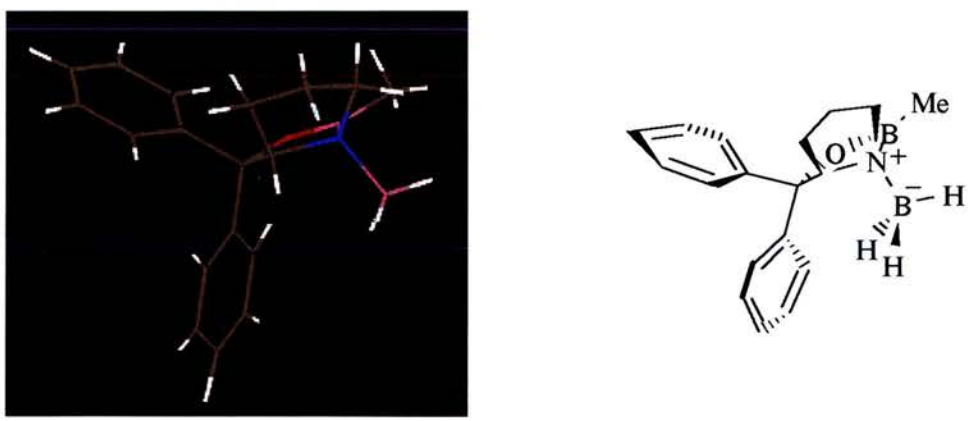
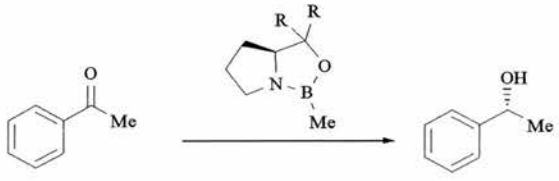


Figure 29 - Crystal Structure of (S)-Methyl-CBS-Oxazaborolidine Complexed to Borane.[8]

This system is widely used for the asymmetric reduction of ketones and Table 14 only shows one or two examples. Corey has recently reviewed a larger number of ketone reductions, showing the effect of changing the reaction conditions.[6] In Corey's review, he has discussed three factors that can improve enantioselectivity, depending on the ketone.[6] These are, using a more bulky amino alcohol, using a

more bulky R group on boron or a more bulky reducing agent. Each of these will be briefly discussed in turn.

Table 15 shows the effect of altering the R group on the oxazaborolidine. **(Scheme 53)**.[6] From the table, the bulk as well as the electronic properties of the R group are important to the enantioselectivity of the reaction.



Scheme 53 - Reduction of Acetophenone with Various Oxazaborolidines.[6]

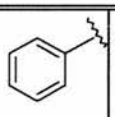
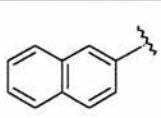
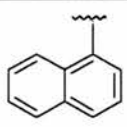
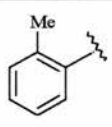
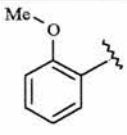
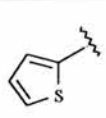
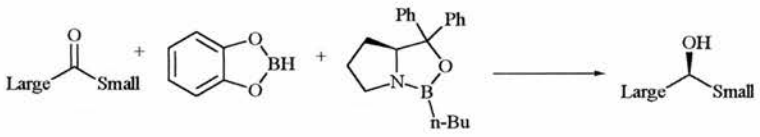
R						
e.e. %	97	98	62	76	28	82

Table 15 - Effect of Oxazaborolidine on the Reduction of Acetophenone.[6]

The above example uses oxazaborolidines with a methyl group on the boron. Alternatively, the group on boron can be changed. From the mechanism, Scheme 51, the group on boron is one of the factors that dictates which way the ketone complexes. This effect should be greater with a larger group on boron, as long as the system is not too sterically hindered. *n*-Butyl is the most common group used instead of the methyl group.[6,10] For example, acetophenone was reduced in 99 % e.e., using n-butyl CBS oxazaborolidine and borane - diethylaniline as the reducing agent.

The last option discussed here is to use a more hindered borane, such as catecholborane **(Scheme 54, Table 16)**.[11] In this case, n-butyl - CBS - oxazaborolidine was also used to increase the enantioselectivities of the reductions.



Scheme 54 - Catecholborane Reduction of a Ketone.[11]

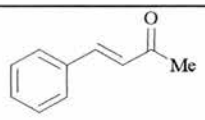
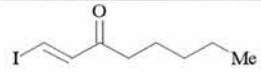
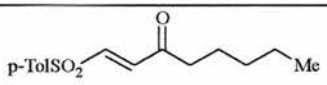
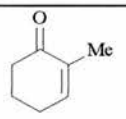
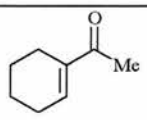
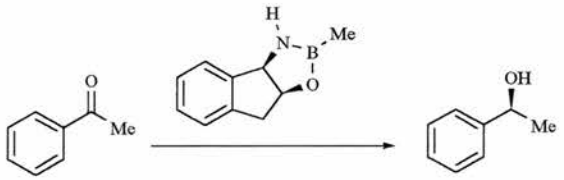
Ketone	Enantiomeric excess %
	92
	86
	91
	93
	81

Table 16 - Enantioselectivities of Various Chiral Reductions using Catacholborane.[11]

Temperature can have a dramatic effect on the enantioselectivity and conversion of the reduction.[12] The effect of temperature is dependent on the oxazaborolidine and ketone used **(Scheme 55, Table 17)**. For example, the optimum for the reduction of acetophenone with the oxazaborolidine in scheme 55 is 0 °C.[12]



Scheme 55 - B-Methyl - (1R) - Amino - (2S) - Indanol and Borane - THF Adduct Reduction of Acetophenone.[12]

Temperature °C	e.e. %	Conversion %
25	77	> 95
0	84	> 95
- 20	50	> 95
- 78	39	12

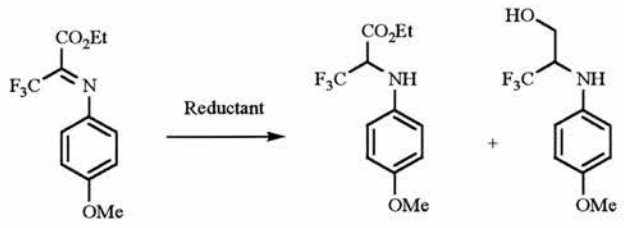
Table 17 - Effect of Temperature on Enantioselectivity and Conversion on the Reduction of Acetophenone.[12]

In the literature, there are many examples of how the reduction conditions can be changed to give the best enantioselectivities. Only a small number of examples have been discussed here. Typically the whole the system has to be optimised for the particular ketone being reduced to get the best enantioselectivities.

5.1.2 Enantioselective Reduction of Imines Using Oxazaborolidines.

Section 5.1.1 discussed the solution reduction of ketones using oxazaborolidines. This system has also been applied in the reduction of imines to secondary amines.

Oxazaborolidines have been used to synthesise chiral fluorinated amino acids.[13,14] These compounds have important roles as suicide inhibitors for a number of pyridoxal - dependent enzymes. Previously, the enantiomers had to be separated by resolution, so an enantioselective preparation was developed **(Scheme 56)**.[13,14]



Scheme 56 - Reduction of Fluorinated Amino Acids.[13,14]

The enantioselective reduction with various oxazaborolidines was studied utilising the above substrate to prepare fluorinated amino acids. Sakai and co-workers showed that the enantioselectivity of the reduction depended on the oxazaborolidine and the borane derivative used. However, even the best reaction conditions only gave an enantiomeric excess of 63 % **(Table 18)**. All the conditions gave the S enantiomer of the alcohol except catecholborane, which gave the opposite enantiomer. Sakai and co-workers gave no further explanation of this observation.[13] There was an added complication that, except for the catecholborane reaction, the ester was also reduced under the reaction conditions employed.

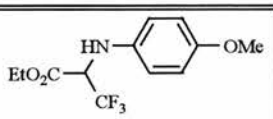
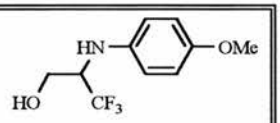
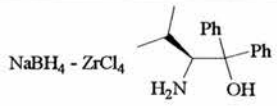
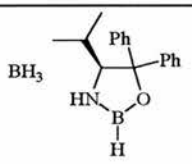
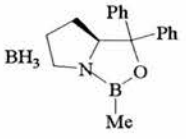
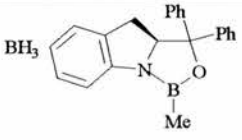
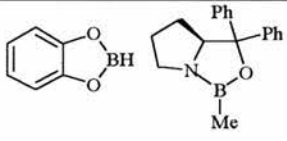
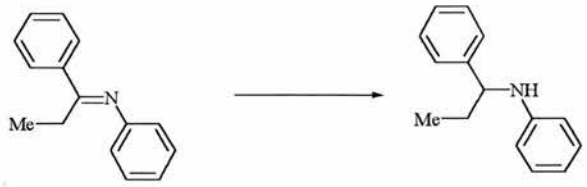
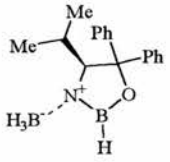
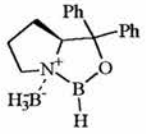
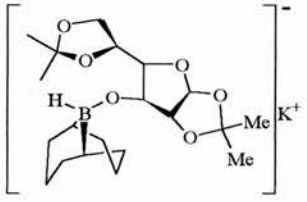
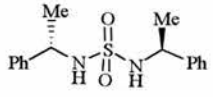
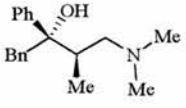
Reductant	Temp / °C				
		Yield / %	e.e. / % (config.)	Yield / %	e.e. / % (config.)
	RT	0	0	95	14 (R)
	RT	40	32 (S)	56	46 (R)
	-78 - RT	42	28 (S)	49	45 (R)
	-78 - RT	38	14 (S)	45	11 (R)
	RT	93	63 (R)	-	-

Table 18 - Effect of Various Oxazaborolidines and reducing agents on the Imine reduction in Figure 54.[13]

However, this imine is very electron withdrawing and therefore, the trends observed in this reduction cannot be directly applied to other imines. The majority of imines do not have such electron withdrawing groups attached.

Alternatively, less electron withdrawing imines have been reduced by oxazaborolidines. For example, the propiophenone *N* - phenylimine was reduced with five different reducing agents, two of which were oxazaborolidines **(Scheme 57)**.[15]



Reducing agent	e.e. / % of amine
 Itsuno's reagent	87
 Corey's reagent	78
	No reduction
$LiAlH_4$ + 	66
$LiAlH_4$ + 	No reduction

Scheme 57 - Effect of Different Chiral Reducing Agents on the Reduction of an Imine.[15]

Scheme 57 demonstrates that out of the chiral reducing agents tried, the oxazaborolidines gave good results whilst Itsuno's reagent was the best. With this promising result from Itsuno's reagent, the effect of the structure of the imines was studied. **(Table 19)**.[15] From table 19, it can be seen that Itsuno's reagent reduces a range of imine with some degree of enantioselectivity. The only imine tried that did

not reduce was the cyclic imine. This may be due to steric factors, with the oxazaborolidine unable to co-ordinate with the imine. The best results were obtained when there is a phenyl group attached to the carbon atom of the imine. Furthermore, if there was also a phenyl group on the nitrogen then the enantioselectivities were increased. When there were only alkyl groups attached to the imine carbon then low enantioselectivities were obtained.

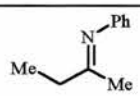
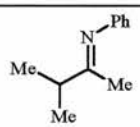
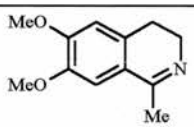
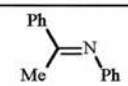
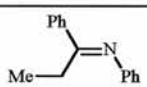
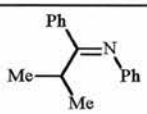
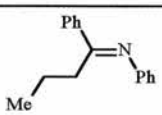
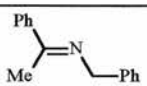
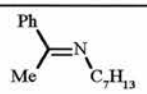
Imine	Time / h	Yield %	e.e. %
	No details given		9
	No details given		14
	No reduction		
	20	98	73
	22	97	87
	24	96	71
	24	97	88
	20	98	46
	20	96	52

Table 19 - The Effect of Imine Structure on the Enantioselective Reduction Using Itsuno's Reagent.[15]

Another study by Cho and co-workers investigated the effect of oxazaborolidine structure on the enantioselectivity of an imine reduction. Six oxazaborolidines and two imines were tested **(Figure 58, Table 20)**.[16]

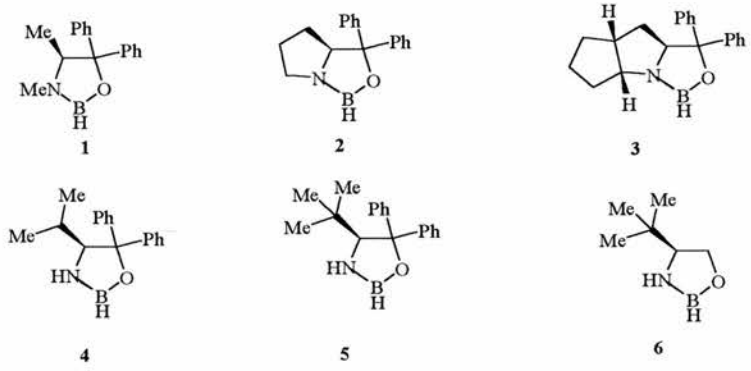
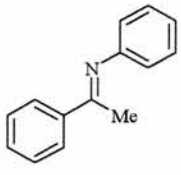
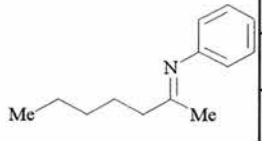


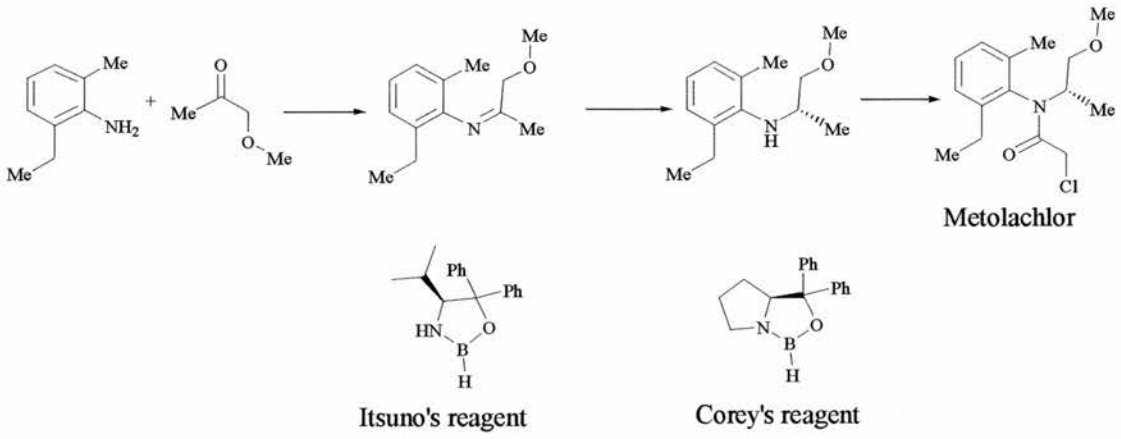
Figure 58 - Various Types of Oxazaborolidines for Imine Reduction.[16]

Compounds	Oxazaborolidine (Fig 58)	Time / h	Amine product		
			Yields %	e.e. %	Config.
	1	8	96	79 (38)[a]	R
	2	3	98	78 (37)[a]	R
	3	2	96	9	S
	4	3	97	73	R
	5	8	94	78	R
	6	2	97	67	R
	1	8	95	13	R
	2	4	91	11	R
	3	8	97	8	S
	4	8	90	18	R
	5	24	87	5	R
	6	4	97	10	R

[a] e.e. in brackets obtained in the presence of 1 equivalents of oxazaborolidine, all other e.e. obtained in the presence of 0.1 equivalents of oxazaborolidine.

Table 20 - Effect of Oxazaborolidine Structure on the Enantioselective Reduction of Imines.[16]

Metolachlor, which is a widely used herbicide, also utilises the enantioselective reduction of an imine in its synthesis. Imine formation followed by the enantioselective reduction with an oxazaborolidine, and finally reaction with an acid chloride gave Metolachlor **(Scheme 59)**.[17]



Scheme 59 - Imine Reduction Using Oxazaborolidines.[17]

Among other reducing agents, Itsuno's and Corey's reagents have been investigated. The final synthesis used Itsuno's reagent. This gave the best enantioselectivities and gave the final amide in 62 % e.e., whereas, if Corey's reagent was used, the amide product was obtained in 52 % e.e.[17] (The actual enantioselectivity of the reduction reaction is not quoted in the literature.)

5.1.3 Polymer Bound Oxazaborolidines.

The disadvantage of the solution phase reduction of ketones with oxazaborolidines is the separation of the catalyst from the product at the end of the reaction.[18] To ease separation and recovery of the oxazaborolidine, some studies into supporting oxazaborolidines onto polymers have been investigated. This has mainly been achieved through the boron, but there are examples of supporting the

oxazaborolidine through an R group on the five membered ring of the oxazaborolidine.

Oxazaborolidines have been supported on various polymeric supports: however, most of these are based on styrene **(Figure 60)**.[18,19,20,21]

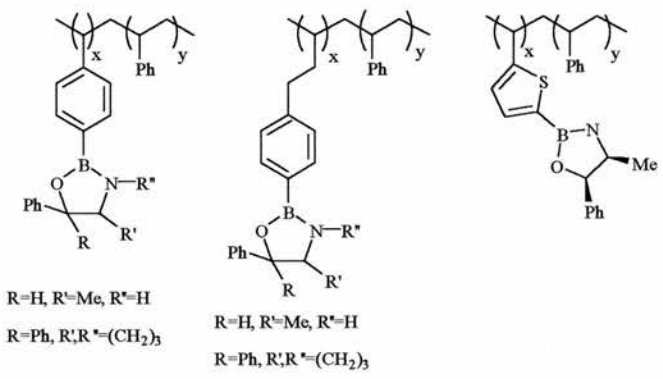
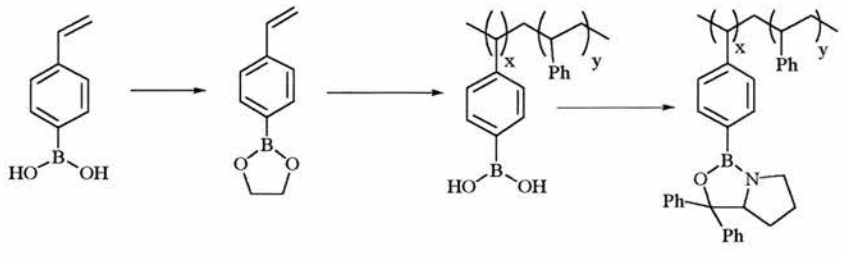


Figure 60 - Examples of Supported Oxazaborolidines.[18,19,20,21]

The boronic acid is first polymerised with a co-monomer and then the oxazaborolidine prepared by reaction with an amino alcohol **(e.g. Scheme 61)**.[20] Before the boronic acid derivative can be polymerised the boronic acid must be protected. This can easily be achieved using 1,2 ethanediol and after polymerisation the free boronic acid can be obtained by treatment of methanol/hydrochloric acid. Refluxing the boronic acid and the amino alcohol in toluene using molecular sieves or Dean - Stark apparatus can then form the oxazaborolidine **(Scheme 61)**.



Scheme 61 - Synthesis of Polymer Bound Oxazaborolidine.[20]

These polystyrene - supported oxazaborolidines give comparable enantioselectivities to those obtained in the homogeneous reaction. The reduction of acetophenone using the catalyst in scheme 61 gave the product with an overall e.e. of 93 %, compared to the homogeneous asymmetric reduction that gave an e.e. of 97 % (Table 14).[20]

Alternatively, the oxazaborolidine can be tethered to the polymer through an R group on the five membered ring **(Figure 62)**.[20, 22,23,24]

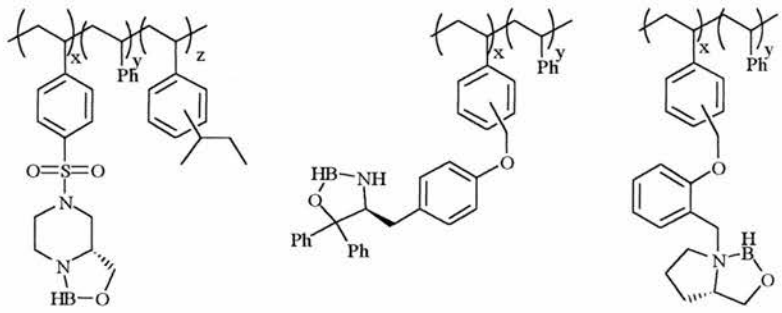
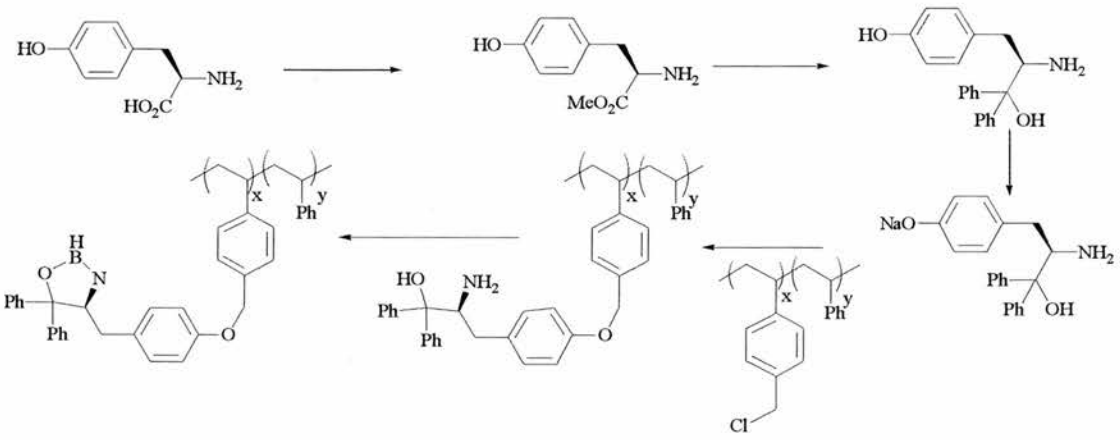


Figure 62 - Polymer Bound Oxazaborolidines.[20,22,23,24]

In one example tyrosine is reacted with phenylmagnesium bromide, followed by supporting the amino alcohol through a linkage involving the phenolic oxygen and finally formation of the oxazaborolidine ring **(e.g. Scheme 63)**.[20,23]

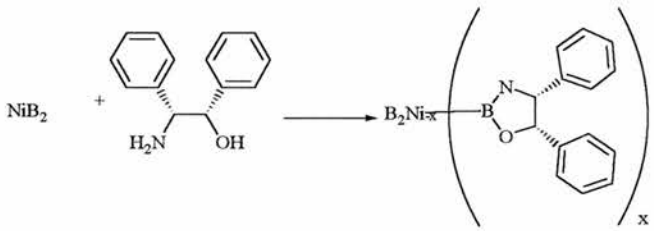


Scheme 63 - Formation of Supported Oxazaborolidine Catalyst.[20,23]

The reduction of acetophenone with the above catalyst gives the chiral alcohol in 91 % e.e. (homogeneous reaction gives an e.e. of 97 % - Table 14).[20]

Supporting the oxazaborolidine catalyst on a polymer support does not reduce the enantioselectivity of the reduction by a significant amount, irrespective of the position at which the oxazaborolidine is bonded.

Oxazaborolidines can also be supported on nickel boride. The boron co-ordinates the amino alcohol **(Scheme 64)**.[25] This system reduces acetophenone with a 94 % e.e. compared to 97 % e.e. with the homogeneous system. However, as with the other supported catalysts, there is a large advantage of the former, as the separation and recycling of the oxazaborolidines is far simpler.



Scheme 64 - Nickel Boride Supported Oxazaborolidine.[25]

All the above examples have used a solid support. Alternatively, a soluble polymer was produced which could be used in a membrane reactor **(Figure 30)**.[26] Using this approach, catalyst 1 reduced acetophenone in 97 % e.e. compared to the solution model oxazaborolidine 2, which reduced acetophenone in 98 % e.e.

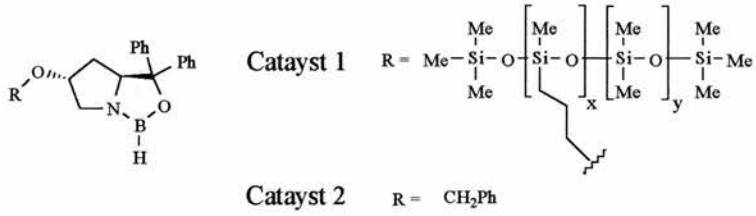


Figure 30 - Soluble Supported Oxazaborolidine for Use in Membrane Reactors.[26]

5.1.4 Aims Of This Study.

- Investigate the solution phase asymmetric reduction of imines and ketones with oxazaborolidines. This includes:
  - Effect of no oxazaborolidine
  - Effect of temperature
  - Effect of reductant
  - Effect of oxazaborolidine

- Investigate the effect of the supported oxazaborolidines (Chapter 2) on the reduction of imine and ketone.

The imine that will be investigated is (1-phenylethylidene)aniline and as a comparison reduction of acetophenone will also be investigated.

5.2 Results and Discussion

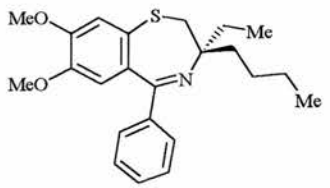
At the beginning of this study, a GlaxoSmithKline intermediate was tested as a substrate for asymmetric reduction using oxazaborolidines. A simpler imine was also investigated as a substrate for asymmetric reductions. The preparation of these imines will be discussed first, followed by the reduction of the GSK imine and finally the reduction of the simple imine. The reduction of acetophenone has also being investigated as a comparison to imine reduction.

5.2.1 Synthesis of Imine Substrates.

The first step was to prepare and purify the imine substrates.

5.2.1.1 Synthesis of (3R)-3-butyl-3-ethyl-7,8-dimethoxy-5-phenyl-2,3-dihydro-1,4-benzothiazepine (GSK imine **(51)**)

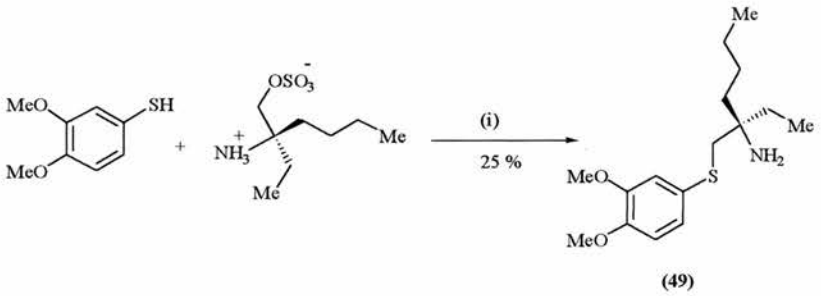
Asymmetric reductions are of interest to GlaxoSmithKline to prepare chiral compounds and drugs. (3R)-3-butyl-3-ethyl-7,8-dimethoxy-5-phenyl-2,3-dihydro-1,4-benzothiazepine (GSK imine **(51)**) is one example of a intermediate that is then reduced, but only one diastereomer is wanted. Therefore, a chiral reduction would be very advantageous, as it would give the diastereomer required without further purification and no waste i.e. the opposite diastereomer will not be discarded.



(51)

The complete synthesis has been developed in house at GlaxoSmithKline for the pilot plant. The first step in the synthesis is to react the thiol with an amino sulphate

to produce (3R)-3-{[(3,4-dimethoxyphenyl)sulfanyl]methyl}heptan-3-amine (amino sulfide) **(49) (Scheme 65)**. The 2,3 dimethoxythiophenol is commercially available, and GlaxoSmithKline buys in the (2 R)-2-ammonio-2-ethylhexyl sulphate from a commercial supplier.



(49)

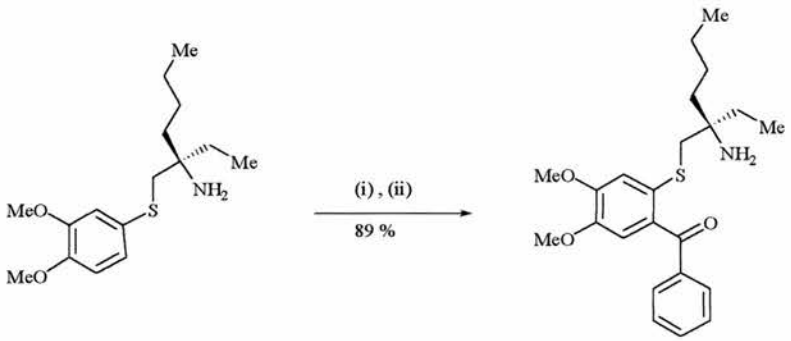
Reagents and conditions: - (i) THF, NaOH (aq), reflux

Scheme 65 – Preparation of (3R)-3-{[(3,4-dimethoxyphenyl)sulfanyl]methyl}heptan-3-amine (49).

The original coupling method used a biphasic system with toluene and aqueous sodium hydroxide. In the mechanism, the sodium hydroxide effects aziridine formation from the amino sulphate. This can then pass from the aqueous phase to the organic phase and react with the thiol. When this procedure was repeated in the lab only disulphide was isolated. In the pilot plant, the stirring speeds are such that the reaction mixture had the consistency of milk and therefore there is good mixing of the phases. However, in the lab, the stirring speeds are far less and the base induced side reaction of disulphide formation predominated. To overcome the problem of stirring speeds, toluene was replaced with THF to give a homogeneous reaction mixture. The amino sulfide was successfully made, although in lower yields, and some disulphide was still isolated.

The next step in the synthesis was to react the amino sulfide **(49)** with benzoyl chloride in the presence of triflic acid to give

(2-{[(2R)-2-amino-2-ethylhexyl]sulfanyl}-4,5-dimethoxyphenyl)(phenyl)methanone (amino benzophenone) **(50) (Scheme 66)**. This was achieved without any problems.

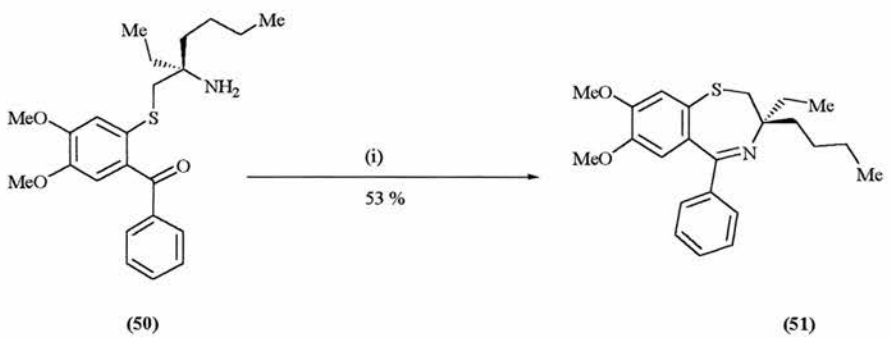


(49) (50)

Reagents and conditions: - (i) Triflic acid, DCM, -10 °C, 40 min; (ii) benzoyl chloride, DCM, reflux 18 h.

Scheme 66 – Preparation of (2-{[(2R)-2-amino-2-ethylhexyl]sulfanyl}-4,5-dimethoxyphenyl)(phenyl)methanone (50)

Finally, an acid induced internal condensation reaction between the amine and ketone to form (3S)-3-butyl-3ethyl-7,8-dimethoxy-5-phenyl-2,3-dihydro-1,4-benzothiazepine (GSK imine **(51)**) was accomplished **(Scheme 67)**



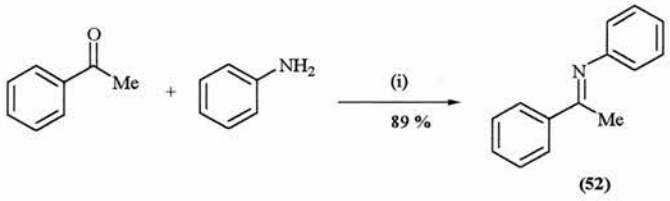
(50) (51)

Reagents and conditions: - (i) Citric acid, toluene, Dean – Stark, reflux, 5 hrs

Scheme 67 – Preparation of (3S)-3-butyl-3ethyl-7,8-dimethoxy-5-phenyl-2,3-dihydro-1,4-benzothiazepine (GSK Imine) (51)

5.2.1.2 Synthesis of (1-phenylethylidene)aniline ***(52).***

The other imine that was investigated was (1-phenylethylidene)aniline (Imine **(52)**). This was prepared in one step by a standard method using titanium (IV) chloride, which acts as a Lewis acid, and a dehydrating agent **(Scheme 68)**.[27]



(52)

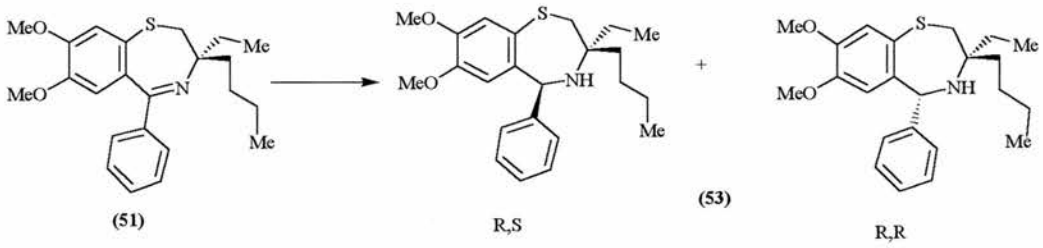
Reagents and conditions: - (i) DCM, Et_3N, $TiCl_4$, 0 °C to RT, overnight.

Scheme 68 – Preparation of (1-phenylethylidene)aniline (52)[27]

Given that imines are reactive and tend to be unstable, the purification of imines can be problematical. One reason that this imine was chosen was that it could be purified easily. Other imines were prepared but it proved very difficult to purify them as they were too air and moisture sensitive. Finally, this imine **(52)** was isolated in 86 % yield by a quick aqueous workup with saturated potassium carbonate to remove the titanium by-products, followed by column chromatography. The column was prepared by first deactivating the silica with triethylamine and the imine was left on the column for as short a period as possible: to aid this, a solvent system was chosen that eluted the imine first. The acetophenone starting material also ran very close to the imine **(52)** but it could be separated, and the amount of acetophenone left after the reaction was kept to a minimum by using an excess of aniline.

5.2.2 Solution Reductions of GlaxoSmithKline Imine.

Once the GSK imine **(51)** had been synthesised, solution reductions were investigated to give (3S)-3-butyl-3ethyl-7,8-dimethoxy-5-phenyl-2,3-tetrahydro-1,4-benzothiazepine (GSK amine) **(53) (Scheme 69, Table 22)**.



Scheme 69 – Reduction of GSK Imine (51) to GSK Amine (53)

Before any reactions could be started, an HPLC system needed to be found that would separate the GSK imine **(51)** and the two diastereoisomers of the GSK amine **(53)**, and this was found using authentic compounds from the pilot plant. The determination of the absolute stereochemistry of the authentic compounds was not available but it was assumed that it was carried out by X-ray diffraction or noe experiments. The HPLC trace below shows that the authentic GSK amine **(53)** actually had an impurity in it, but this did not interfere with the peaks of interest **(Figure 31)**.

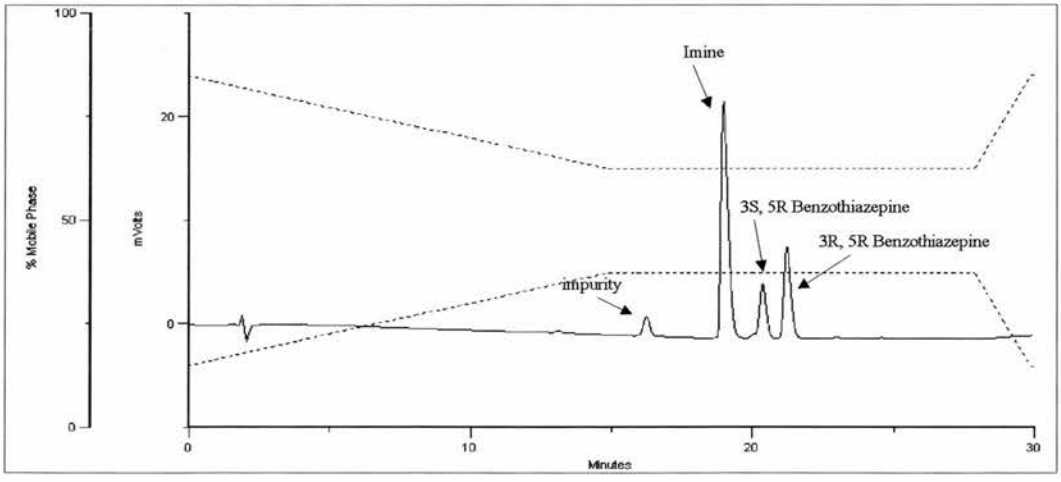


Figure 31 – HPLC Trace to Show the GSK Imine (51) and GSK Amine (53).

It was found that the GSK Imine **(51)** and the two diastereomers of the GSK Amine **(53)** separated using a Prodigy 5 μ ODS column which was 150 x 4.6 mm in size. To

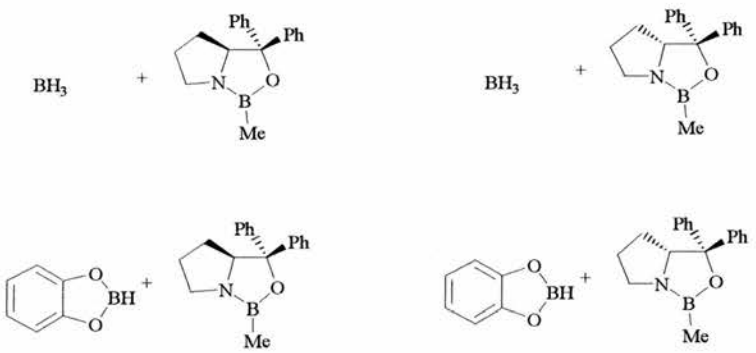
obtain a good separation a flow rate of 1 ml min^{-1} and a solvent gradient was used. The two mobile phases were water/ acetonitrile/TFA (95:5:0.1) (Aqueous phase) and water/acetonitrile (5:95) (organic phase). The HLPC run started off at 85 % aqueous phase, went to 62.5 % in 15 min and stayed at this for13 min and then went back to 85 % in 2 min: total run time of 30 min. To obtain accurate e.e. the absorbance of the peaks from the HPLC trace needed to be between 0.1 and 1. 20 μl of a 0.25 mg ml^{-1} solution of the GSK imine **(51)** produced peaks on the HPLC trace of the required intensity.

The GSK imine **(51)** gave a peak of approximately double the intensity of the equivalent amount of GSK amine **(53)** at 215 nm. This is because the GSK imine **(51)** has a stronger absorption at this wavelength, as there is more conjugation. The conjugation is partially lost when the GSK imine **(51)** double bond is reduced. This trace gives baseline separation for all the peaks and all the compounds elute from the column in a reasonable length of time. The longer the peaks take to come off the column the broader the peaks are going to be, as the bands for each compound will diffuse on the column and the peaks will start to merge. If the mixture is not on the column long enough then there is not sufficient time for the compounds to interact with the column and baseline separation will not be obtained. The column packing and solvent system/ gradient will obviously also determine the separation. (See the section 5.3 for the HPLC conditions.)

Initially, the GSK imine **(51)** was reduced with sodium borohydride.[28] This required a catalytic amount of glacial acetic acid for the reduction to work. This gave the expected 55:45 ratio of the diastereoisomers which had been found previously at GSK. Borane-Pyridine adduct was then used for the reduction of the GSK imine

(51), as a better model for borane used in the asymmetric reductions.[29] This also required glacial acetic acid but the reaction was completed in 3 hours compared to the sodium borohydride reaction that took 5 hours. The same diastereomeric ratio was obtained.

Once these reductions had been investigated, some chiral reductions with oxazaborolidines were tried. Various conditions and reducing reagents were tried, and these are shown in **Scheme 70 and Table 22.**



Scheme 70 – Various Reducing Reagents for Chiral Oxazaborolidine Reductions.

Reducing agent	time/ hrs	HPLC peak % GSK imine (51):R,S:R,R[a]	Diastereomeric ratio R,S:R,R
Sodium borohydride	5	0:54:46	54:46
Borane pyridine adduct	3	0.18:54:46	54:46
(S)-methyl-CBS-oxazaborolidine (0.1 equiv.) and Borane	1	51:27:22	55:45
(S)-methyl-CBS-oxazaborolidine (1 equiv.) and Borane	18	19:43:34	56:44
(R)-methyl-CBS-oxazaborolidine (0.1 equiv.) and Borane	1	60:21:19	52:48
(S)-methyl-CBS-oxazaborolidine (0.1 equiv.) and Catecholborane	18	0.48:51:48	52:48
(R)-methyl-CBS-oxazaborolidine (0.1 equiv.) and Catecholborane	18	0.3:52:47	52:48

[a]HPLC peak due to GSK imine **(51)** gives ~ double the % of the same amount of GSK amine **(53)**.

Table 22 – Results for Solution Reduction of GSK Imine (51)

The most common conditions for oxazaborolidine catalysed reductions use 0.1 equivalents of the oxazaborolidine with borane – THF adduct.[4,5,15] These conditions were tried and no enantioselectivity was observed; therefore, the amount of the oxazaborolidine was increased, but this did not improve the enantioselectivity. One explanation for this was that the stereogenic centre next to the GSK imine **(51)** bond might be interfering with the complexation of the (S)-methyl-CBS-oxazaborolidine, which had been used. Using (R)-methyl-CBS-oxazaborolidine could determine if this was occurring, because if the (S)-methyl-CBS-oxazaborolidine was giving a mismatched pair with the GSK imine **(51)**, then (R)-methyl-CBS-oxazaborolidine would give the matched pair. This proved not to be the case, as no enantioselectivity was seen with the (R)-methyl-CBS-oxazaborolidine reduction either. Sakai and co-

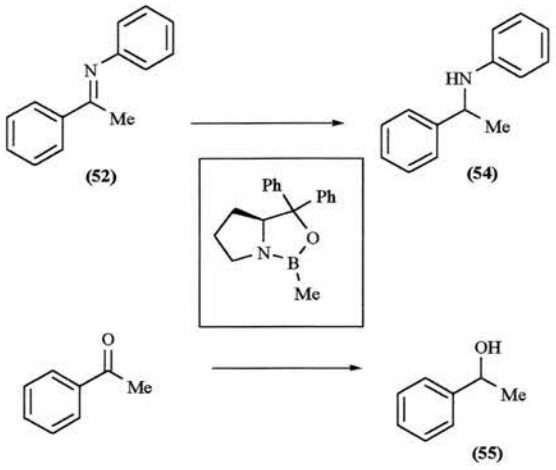
workers had shown, with imine reductions, that if borane THF did not give good enantioselectivity then catecholborane sometimes improved the asymmetric induction of the reduction.[11,13] Unfortunately, when the chiral reductions were carried out with either (S) or (R) methyl CBS oxazaborolidine and catecholborane, only the uncatalysed reduction was observed to give the expected diastereomeric ratio of approximately 55:45.

In all the above oxazaborolidine reductions only the uncatalysed reduction was observed. Therefore, the borane or catecholborane is reducing the GSK imine **(51)** but the oxazaborolidine is not playing a part in the reduction. This implies that the GSK imine **(51)** is not complexing to the oxazaborolidine, which is backed up by the reduction being slow. Typically, a reduction with oxazaborolidine and borane only takes a few minutes for a complete conversion. This cyclic GSK imine **(51)** is probably too hindered to come close enough to co-ordinate with the boron of the oxazaborolidine.

5.2.3 Solution Reductions of Phenyl - (1 - Phenyl - Ethylidene) – Amine (52) and Acetophenone in the Absence of Oxazaborolidine.

5.2.3.1 Reduction with Sodium Borohydride and Borane-pyridine Adduct.

Although the GSK imine **(51)** does not seem to be complexing with the oxazaborolidine, we were still interested in oxazaborolidine catalysed imine reduction. Phenyl-(1-phenyl ethylidene)-amine **(52)** was chosen because it has been quoted in the literature to be asymmetrically reduced by Itsuno's reagent, and as already discussed it could be easily prepared.[15] For comparison with a well documented system we also examined acetophenone reduction **(Scheme 71)**; the raw data are shown in appendix 6.7.



Scheme 71 - Reductions of Imines and Ketones using (S) Methyl CBS Oxazaborolidine.

As with the GSK imine **(51)**, both the imine **(52)** and acetophenone were first reduced with sodium borohydride and borane - pyridine complex. Both these reducing agents gave the expected racemic products **(Table 23)**.

Substrate	Reductant	Time (hrs)	Yield (%)
Imine **(52)**	Sodium borohydride	5	91
	Borane pyridine	4	79
Acetophenone	Sodium borohydride	5	68
	Borane pyridine	4	63

Table 23 – Results from the Uncatalysed reduction of Imine (52) and Acetophenone.

The racemic amine **(54)** (and alcohol **(55)**) produced from these reactions were then used as standard solutions for determining the HPLC conditions.

5.2.3.2 HPLC conditions for imine ***(52)*** *and acetophenone reductions.*

As we are starting with a molecule with no other stereogenic centres, the products are enantiomers and therefore chiral HPLC had to be used. Figure 32 and 33 show a typical HPLC trace for a mixture of substrate and product for both imine **(52)** and acetophenone reactions. These are the simplest HPLC traces obtained and later on in the discussion other HPLC traces will be shown where other peaks due to side reactions appear. The assignments of the peaks were made by the comparison of the sign of the optical rotation.[30,31] From the literature,[30] the optical rotation for the R enantiomer of phenyl-(1-phenyl-ethyl)-amine was – 17.6. To assign the HPLC trace the optical rotation of the amine **(54)** was recorded. As the imine **(52)** could not be reduced in 100 % e.e. the optical rotation was recorded of the mixture of the two enantiomers of the amine **(54)**. The sign of the observed optical rotation is the sign of the optical rotation of the major enantiomer present, which was seen by HPLC. The optical rotation is not large enough to give accurate e.e. so the HPLC was used for this. A similar method was used for 1-phenyl ethanol.[31]

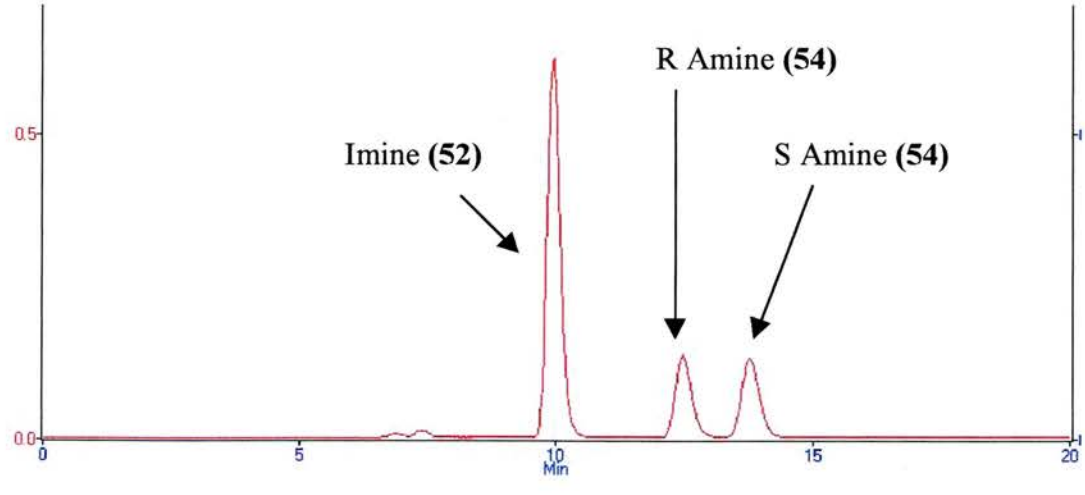


Figure 32 - HPLC Trace for (1-phenylethylidine)analine (52) and N-(1-methylbenzyl)analine (54) at 254 nm

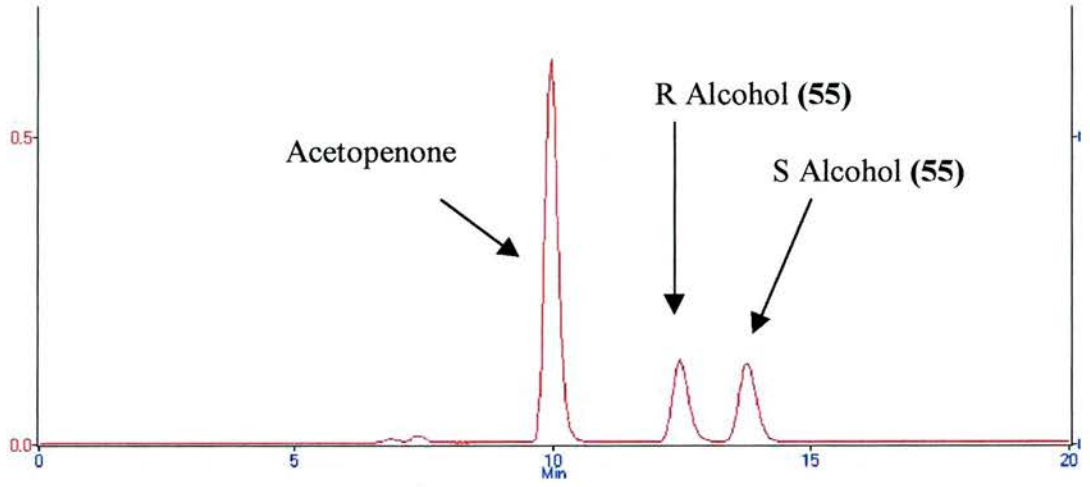


Figure 33 - HPLC Trace for Acetophenone and 1-Phenylethanol (55) at 215 nm

To get accurate conversions and e.e's it was determined that for the imine reduction the HPLC trace had to be recorded at 254 nm and for the acetophenone reduction at 215 nm. The conversion was calculated by dividing the sum of the integrals of the two enantiomers of the amine **(54)** by the integral of the imine **(52)** and multiplying by 100. This would only give the correct conversion if the absorptions of imine and amine were the same i.e. the integral of the imine equals the integral of the amine of the same concentration. When calibration graphs were plotted, it was found that the graph could be fitted to several trend lines (e.g. linear, power series and polynomial) all within 10 % of the uncorrected conversions. Therefore, the uncorrected conversions have been used and quoted in this thesis. The calibration graphs have been recorded in Appendix 6.6 and the same applies to the ketone reductions.

Unless stated all the reductions were carried out in the presence of 0.1 equivalents oxazaborolidine. This was because if 1 equivalent oxazaborolidine was used then the reaction could not be followed by the HPLC method. This was because the peak from the oxazaborolidine overlapped with one of the peaks from the amine product. In the absence of oxazaborolidine the reduction gives the racemic product and

therefore the e.e. will be zero. However, when the reduction was run in the absence of oxazaborolidine the e.e.'s calculated from the HPLC showed some enantioselectivity. This will be the error in the HPLC method and therefore the e.e.'s quoted are the corrected values which means the e.e. values obtained when no oxazaborolidine was present have been subtracted from the observed e.e. (See section 5.2.4.1.1)

The HPLC results have been divided into several sections. All the various conditions have been investigated for both imine and ketone reduction and these will be discussed separately. Within each of these sections there are three distinct subsections and these are shown below.

1. Solution phase reductions:
   - Solution phase reduction with no oxazaborolidine present – sections 5.2.4.1.1 (imine) and 5.2.5.1.1 (ketone).
   - Solution phase reduction with (S) methyl CBS oxazaborolidine at different temperatures – sections 5.2.4.1.2 (imine) and 5.2.5.1.2 (ketone).
   - Solution phase reduction with (S) methyl CBS oxazaborolidine with different reductants – sections 5.2.4.1.3.3 (imine) and 5.2.5.1.3 (ketone).
   - Solution phase reduction with (S) phenyl oxazaborolidine with different reductants – sections 5.2.4.1.4 (imine) and 5.2.5.1.4 (ketone).
   - Solution phase reduction with (S) methyl CBS oxazaborolidine but changing the order of addition. – section 5.2.4.1.5 (imine) and 5.2.5.1.4 (ketone).

2. Solution phase reductions in the presence of silicates.

- Effect of molecular sieves on solution phase reduction with (S) methyl CBS oxazaborolidine – sections 5.2.4.2.1 (imine) and 5.2.5.2.1 (ketone).
- Effect of MCM-41 **(1)** on solution phase reaction with (S) methyl CBS oxazaborolidine – sections 5.2.4.2.2 (imine) and 5.2.5.2.2 (ketone).
- Effect of Silica on solution phase reaction with (S) methyl CBS oxazaborolidine – sections 5.2.4.2.3 (imine) and 5.2.5.2.3 (ketone).
- Effect of MCM-41 and silica supported boronic acid on solution phase reduction with (S) methyl CBS oxazaborolidine – sections 5.2.4.2.4 (imine) and 5.2.5.2.4 (ketone).

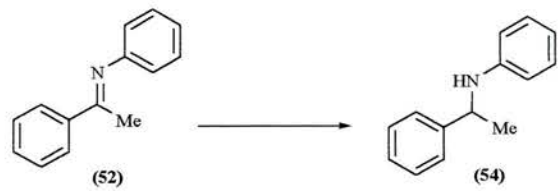
3. Solid Supported oxazaborolidines.

- 0.1 equivalents and 1 equivalent of polymer supported oxazaborolidines with various reductants – sections 5.2.4.3.1 (imine) and 5.2.5.3.1 (ketone).
- 0.1 equivalents and 1 equivalent of MCM-41 supported oxazaborolidines with various reductants – sections 5.2.4.3.2 (imine) and 5.2.5.3.2 (ketone).
- 0.1 equivalents and 1 equivalent of silica supported oxazaborolidines with various reductants – sections 5.2.4.3.2 (imine) and 5.2.5.3.2 (ketone).
- Effect of changing the order of addition using 0.1 equivalents of MCM-41 supported oxazaborolidine with various reductants – sections 5.2.4.3.3 (imine) and 5.2.5.3.3 (ketone).

5.2.4 Asymmetric reductions of Phenyl - (1 - Phenyl - Ethylidene) – Amine (52).

5.2.4.1 Investigation into solution phase asymmetric imine reduction.

Table 24 shows the results obtained from the solution phase studies in asymmetric reduction of imine **(52)** after 1 hour.



(52) (54)

Reductant[a]	Catalyst[b]	e.e./ % (Config.)[c]	Conversion/ %
BTHF	None	0	91
CB		0	87
BDMS		0	95
BTHF	A	69 (R)	87
BTHF		1 (R) [d]	92
BTHF		2 (R) [e]	90
CB		47 (S)	98
CB	B	49 (R)	91
BDMS	A	9 (S)	> 99
BTHF	C	81 (R)	30
CB		10 (R)	85
BDMS		4 (R)	97
BTHF	A[f]	0	54
CB		3 (S)	92
BDMS		2 (R)	99

[a]BTHF = Borane THF adduct, CB = Catecholborane, BDMS = Borane DMS adduct. [b]A = (S) methyl CBS oxazaborolidine, B = (R) methyl CBS oxazaborolidine, C = phenyl oxazaborolidine, [c]from comparison with optical rotation.[30] [d] Run at 0 °C, [e] Run at –78 °C, [f] Order of addition changed - see section 5.2.4.1.5

Table 24 – Solution Phase Imine Reductions after 1 hour.

5.2.4.1.1 Effect of no oxazaborolidine.

The reductions were first run without any oxazaborolidine present to see what the effect of the uncatalysed reaction was. 1.2 equivalents of borane - THF and borane - DMS or 2 equivalents of catecholborane were used. A larger amount of catecholborane was used because unlike the other boranes, catecholborane only has one transferable hydrogen.

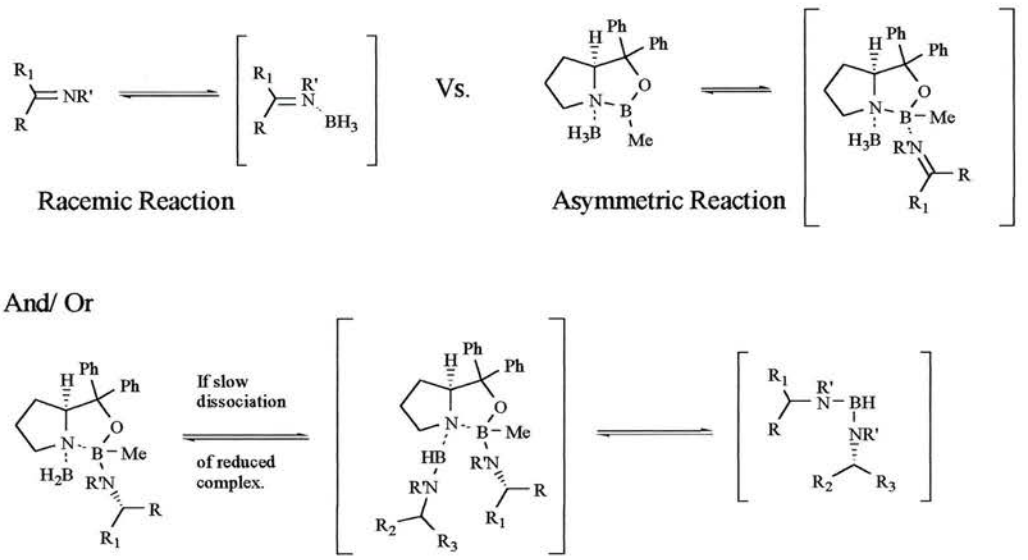
The imine **(52)** will reduce rapidly without oxazaborolidine present and this will cause problems when the asymmetric reaction is investigated. If the uncatalysed reaction is fast then it will significantly compete with the catalytic asymmetric reaction. From table 12 it can be seen that the e.e. quoted is less than 20 % and this seems to be the amount of error in this HPLC method, as the optical rotation of this product was zero. This is a good indication that the product is racemic however, the expected optical rotation for a 20 % e.e. would be – 3.5 so the errors in this reading would also be large and therefore it is not conclusive.

5.2.4.1.2 Effect of temperature.

The asymmetric imine reduction was tried at room temperature, 0 °C and –78 °C using borane THF as the reductant. It was found that at room temperature, the asymmetric reaction took place, and after 60 min an e.e. of 69 % and a conversion of 87 % was obtained. However, lowering the temperature had a detrimental effect on the enantioselectivity of the reaction and only the uncatalysed reaction occurred.

As already discussed in section 5.1.1, there are many different equilibria involved in this system. The balance of these equilibria determine whether or not the asymmetric reaction dominated. In the case of imine reduction, lowering the temperature

disfavours the equilibrium associated with the asymmetric reaction. There could be two possible explanations for this based on the proposed mechanism shown in **(Scheme 72)**.



Scheme 72 – Two Possible Equilibria that could determine the Extent of Asymmetric Imine Reduction.

Firstly, at lower temperatures the complex of the imine with oxazaborolidine may be disfavoured over the complex between the imine and borane alone and this would then lead to the uncatalysed reaction. On the other hand it could be that once the imine has been reduced, the complex does not dissociate quickly at lower temperatures. If this was the case this species is still capable of reducing another imine but no co-ordinating to oxazaborolidine so that the second reduction gives the racemic product. The latter mechanism is perfectly plausible but alone would not produce a racemic mixture so other processes are also taking place. If the latter mechanism does occur, it can be reasonably assumed, that this effect will be greater for imines than for ketones because nitrogen has a greater affinity for boron compared to oxygen.

5.2.4.1.3 Effect of reducing agent.

Table 14 shows the results after 60 min. As can be seen in the appendix the reductions were studied at different time points: these were 1, 3, 5, 60, 120, 180, 240 and 300 min. These time points allowed investigation into what occurs within the first 5 min and over a longer time period. Due to the result obtained from the temperature experiments the rest of the reductions investigated were carried out at room temperature. The next step was to see the effect of different borane reductions. The three boranes were borane THF, catecholborane and borane DMS, and these have all been used in the literature with oxazaborolidines. Borane THF has already been tested at room temperature and after 60 min gave an e.e of 69 % and conversion of 87 %. In fact, this result was obtained after 5 minutes with no real change in conversion or enantioselectivity after that. As already seen, the uncatalysed reaction gives approximately 80 % conversion after 1 minute. In the presence of oxazaborolidine the rate of conversion is slower overall. Usually a catalyst increases the rate of reaction however, in this system the catalyst lowers the rate of reaction. This again must be due to a shift in the balance of the various equilibria. From the HPLC results the reduction before 3 min only gives racemic product however after 3 min the asymmetric reduction starts to become dominant until after 5 min an e.e. of 69 % is obtained. The exact reason for this is not fully understood. From the results obtained, if a conversion over 80 % is obtained then the uncatalysed reduction is favoured and dominates.

The next reductant tested was catecholborane. This is a bulky reductant and has been found sometimes to improve the enantioselectivity of the reaction. When the reduction was carried out in the presence of (S) methyl CBS oxazaborolidine (as with borane THF) the opposite enantiomer (i.e. S) was obtained. The e.e. was also lower

than observed with borane THF. To check this result was correct the reduction was also carried out with (R) methyl CBS oxazaborolidine. This backed up the original result, as it gave the R enantiomer.

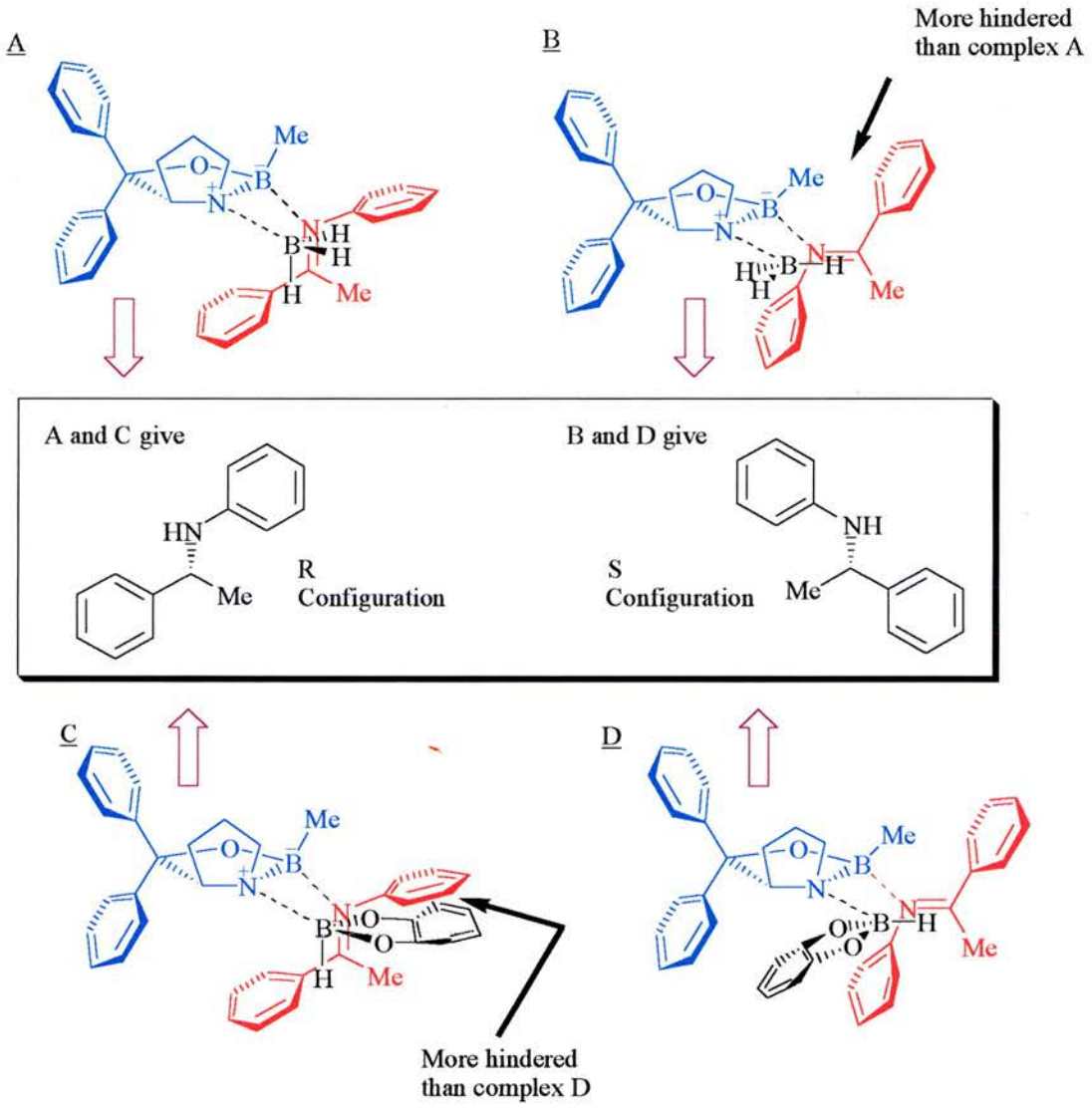


Figure 34 - Transition State Model for Reduction with borane THF and Catecholborane.

This result can be explained if a model of the complex is made **(Figure 34)**. The two constraints that have been made are that the imine **(52)** is in the *trans* conformation and the resulting complex has the imine **(52)** double bond and one of the B-H bonds

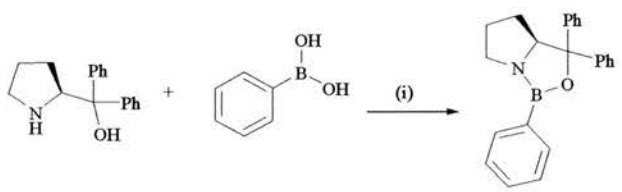
parallel. The difference between borane - THF and catecholborane, is that catecholborane is much more hindered. Looking at the possible complexes **(Figure 34 A and B)**, borane - THF adduct is small enough not to interfere with how the imine **(52)** co-ordinates with the oxazaborolidine. Therefore, the least hindered complex is formed, which is A, and gives the R configuration of the amine. When borane - THF adduct is replaced with catecholborane, the catecholborane clashes with the phenyl ring on the nitrogen of the imine **(52) (Figure 34 C)**. Alternatively, the imine **(52)** can be rotated by 180°, into the slightly more hindered conformation. The catecholborane can then be complexed without clashing with the imine **(52) (Figure 34 D)**. Overall, this gives a less hindered system compared to complex C, as the catecholborane no longer clashes with the imine. This rotation means that the other face of the double bond is presented to the catecholborane and therefore, the opposite enantiomer is formed.

The last borane tested was borane DMS. When this was tested a racemate was again obtained. This result is odd because as THF is the solvent and therefore in large excess to the borane DMS, then borane DMS should convert to borane THF. Certainly when no oxazaborolidine is present they behave the same. However, in the presence of oxazaborolidine the borane THF undergoes the asymmetric reaction whereas borane DMS does not.

5.2.4.1.4 Effect of phenyl oxazaborolidine

All the work so far had used (S) methyl CBS oxazaborolidine that is commercially available. However, the proposed solid supported oxazaborolidines that were going to be prepared and tested all had a phenyl substituent attached to the boron of the oxazaborolidine (See chapter 2). Therefore, (S) phenyloxazaborolidine was prepared

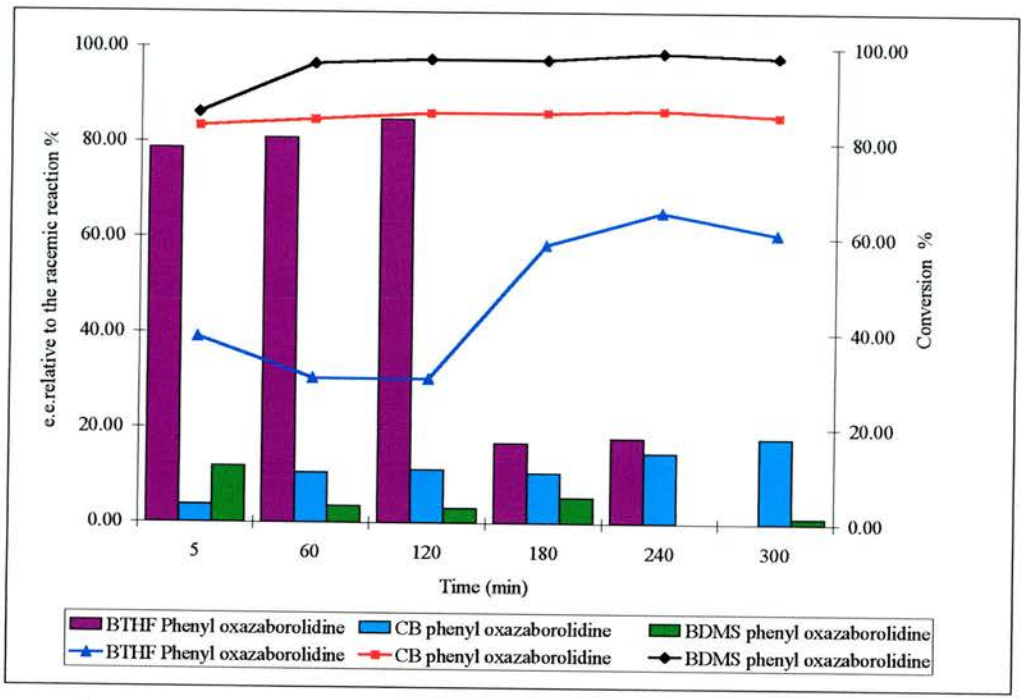
by a modified preparation reported by Corey and co-workers[4] and tested as a solution model for the solid supported oxazaborolidines. (S) Phenyloxazaborolidine was prepared by refluxing (S) α,α - diphenylprolinol with phenyl boronic acid in toluene in the presence of molecular sieves **(Scheme 73)**. After 18 hrs refluxing the solution was used directly in the test imine reductions.



Reagents and conditions: - (i) Toluene, molecular sieves, reflux 18 h.

Scheme 73 – Preparation of (S) phenyloxazaborolidine.[4]

This oxazaborolidine was then tested in the asymmetric reduction of imine **(52)** in the presence of the three different reductants. It was found that with borane THF, an e.e. of 81 % and a conversion of 30 % were obtained within 60 min. However, after 180 minutes only the racemic product was observed and this coincided with a rise in conversion **(Chart 1)**. In this system it appears that the oxazaborolidine is active but after approximately 180 min the oxazaborolidine is deactivated and only the uncatalysed reaction occurs. As seen with (S) methyl CBS oxazaborolidine the uncatalysed reaction is faster than the asymmetric reaction. Catecholborane and Borane DMS gave no asymmetric reaction in the presence of (S) phenyl oxazaborolidine and only the uncatalysed reaction occurred. Catecholborane may be too large with this bulky oxazaborolidine to form the complex. Borane DMS gave the same result as with (S) methyl CBS oxazaborolidine but the explanation for the difference compared to borane THF is unclear. Both reactions are run in THF so it can be reasonably assumed that the borane DMS would convert to borane THF.



e.e. = bars, conversions = lines.

Chart 1 – Effect of (S) phenyl oxazaborolidine on imine (52) reduction.

5.2.4.1.5 Effect of changing the order of addition.

So far the order of addition for the asymmetric reductions has been to add the imine **(52)** and the oxazaborolidine together in THF and stir for 10 min and then to add the borane. This gives time for the oxazaborolidine and imine to complex before the borane is added. The alternative is to add the borane and oxazaborolidine together first followed by the imine 10 min later. When this order of addition was tried only racemic product was obtained. This is probably due to the fact that the uncatalysed reaction is so fast. If the imine and oxazaborolidine are pre - mixed then there is time for the oxazaborolidine and imine to complex before any reducing agent is added. However, if the borane and oxazaborolidine are pre - mixed and then the imine added the imine will be reduced by the excess free borane before the imine has time to complex to the oxazaborolidine. This assumes that the imine complexing to the oxazaborolidine is slower than the rate of the uncatalysed reduction.

5.2.4.2 Investigation into the effect of silicates on the solution phase asymmetric imine reduction.

The effect of various silicates on the asymmetric reduction of imines was investigated using (S) methyl CBS oxazaborolidine and the three boranes already mentioned. Table 25 show the results obtained after 1 hour.

The different silicates used were 4 Å powered molecular sieves, MCM-41 **(1)** , silica, MCM-41 supported boronic acid **(30)** and silica supported boronic acid **(31)**.

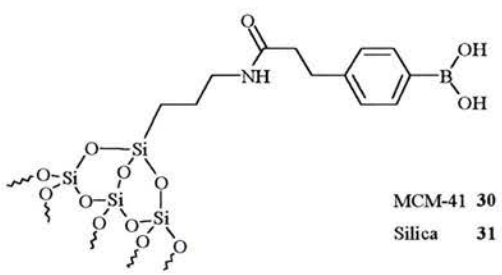


Figure 35 – Structure of MCM-41 and silica supported boronic acid (30 and 31).

Reductant[a]	Other conditions	e.e./ % (Config.)[b]	Conv./ %
BTHF	No silicate added	69 (R)	87
CB		47 (S)	98
BDMS		9 (S)	> 99
BTHF	Molecular sieves	6 (S)	69
CB		3 (S)	94
BDMS		3 (R)	99
BTHF	20 mg MCM-41 **(1)**	0	67
CB		15 (S)	92
BDMS		7 (S)	98
BTHF	200 mg MCM-41 **(1)**	4 (R)	68
CB		12 (S)	85
BDMS		10 (R)	97
BTHF	50 mg Silica	0	67
CB		22 (S)	90
BDMS		3 (S)	98
BTHF	500 mg Silica	7 (R)	46
CB		10 (S)	68
BDMS		0	89
BTHF	MCM-41supported boronic acid **(30)**	19 (S)	64
CB		13 (S)	93
BDMS		10 (S)	99
BTHF	Silica supported boronic acid **(31)**	1 (S)	83
CB		15 (S)	86
BDMS		15 (S)	98

[a]BTHF = Borane THF adduct, CB = Catecholborane, BDMS = Borane DMS adduct. [b]from comparison with optical rotation.[30]

Table 25 – Effect of silicates on the solution phase asymmetric imine reduction.

5.2.4.2.1 Effect of molecular sieves on the solution phase imine reduction

Oxazaborolidine catalysed reductions are moisture sensitive and therefore, the effects of freshly activated molecular sieves were tested. As seen with the solution phase studies, slight variations can completely kill the asymmetric reaction. The addition of molecular sieves was detrimental to the asymmetric reaction and only the uncatalysed reaction was observed. Molecular sieves are basic and in this instance seem to be preventing the complexation of the imine and oxazaborolidine or at any rate slowing it down. On the other hand they do not seem to affect the borane complexing to the imine, as the borane is still reducing the imine.

5.2.4.2.2 Effect of MCM-41 **(1)** on the solution phase asymmetric imine reduction.

The effect of MCM-41 **(1)** was tested with a small amount of MCM-41 **(1)** and a slurry (200 mg) of MCM-41 **(1)** to see the effect that it has on the solution phase asymmetric reaction. Irrespective of the amount of MCM-41 **(1)** added the uncatalysed reaction dominates and only racemic product is observed. In this reaction the MCM-41 **(1)** was added at the start with the imine and oxazaborolidine. If the MCM-41 **(1)** affects the complexation of the imine and oxazaborolidine then this would indeed give the result observed. This could be a problem later on using MCM-41 **(1)** as a support for the oxazaborolidines but there are ways around this that will be discussed later.

5.2.4.2.3 Effect of silica on the solution phase asymmetric imine reduction.

Not surprisingly the same results as observed for MCM-41 **(1)** were observed here. With borane DMS in the presence of the silica slurry there was an instantaneous large amount of gas released on the addition of the borane. This will be discussed

later with respect to the acetophenone asymmetric reduction in the presence of MCM-41 **(1)** and silica.

5.2.4.2.4 Effect of MCM-41 or silica supported boronic acid **(30 and 31)** on the solution phase asymmetric imine reduction.

These experiments were carried out mainly as a control for the solid supported oxazaborolidine reactions. As the solid supported oxazaborolidines still have some free boronic acids (seen from the loading, see chapter 2), the effect of the presence of boronic acid was determined. There was a possibility that there would be exchange of the prolinol from (S) methyl CBS oxazaborolidine to the solid supported boronic acids. This could affect the asymmetric reduction. When the reductions were run both MCM-41 **(1)** and silica behaved the same and only the uncatalysed reaction was observed. This could be due to exchange, already mentioned, but is probably just because there is MCM-41 **(1)** or silica present. As already seen this has a detrimental effect.

5.2.4.3 Effect Of Solid Supported Oxazaborolidines on Asymmetric Imine Reduction.

After the solution phase reductions had been investigated the effect of solid supported oxazaborolidines was tested. The preparations of these solid supported oxazaborolidines have been discussed in chapter 2. As the oxazaborolidine is not in solution then as well as 0.1 equivalent oxazaborolidine, 1 equivalent could also be tested as this does not interfere with the HPLC. The solid supported oxazaborolidines tested were polymer, MCM-41 and silica supported oxazaborolidines all with the S configuration.

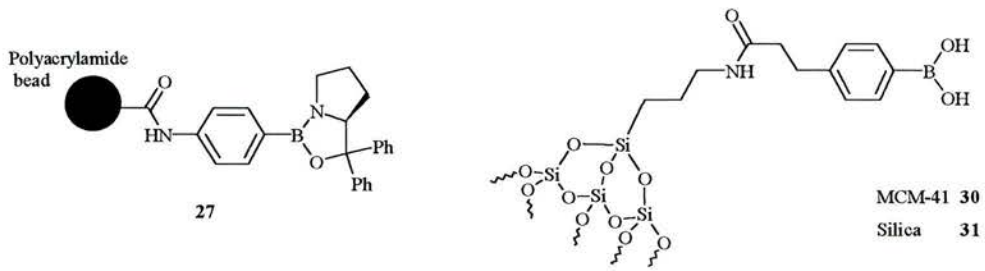


Figure 36 – Structures of solid supported oxazaborolidines that have been prepared (Chapter 2).

Reductant[a]	Catalyst[b]	e.e./ % (Config.)[c]	Conv./ %
BTHF	Homogeneous reduction	69 (R)	87
CB		47 (S)	98
BDMS		9 (S)	> 99
BTHF	0.1 equivalents A	3 (R)	68
CB		12 (S)	97
BDMS		2 (S)	98
BTHF	1 equivalent A	11 (S)	54
CB		14 (S)	92
BDMS		5 (S)	94
BTHF	0.1 equivalents B	5 (R)	66
CB		2 (S)	97
BDMS		6 (S)	> 99
BTHF	1 equivalent B	Could not be determined see section 5.2.4.3.2	
CB			
BDMS			
BTHF	0.1 equivalents C	18 (S)	70
CB		16 (S)	97
BDMS		14 (S)	99
BTHF	1 equivalent C	Could not be determined see section 5.2.4.3.2	
CB			
BDMS			
BTHF	0.1 equivalents B[d]	4 (S)	86
CB		16 (S)	89
BDMS		8 (S)	95

[a]BTHF = Borane THF adduct, CB = Catecholborane, BDMS = Borane DMS adduct. [b] A = polyacrylamide supported oxazaborolidine **(27)**, B = MCM-41 supported oxazaborolidine **(32)**, C = silica supported oxazaborolidine **(33)** [c]from comparison with optical rotation.[30] [d] Change in order of addition –see section 5.2.4.3.3

Table 26 – Effect of solid supported oxazaborolidines on the asymmetric imine reduction after 1 hour.

5.2.4.3.1 Effect of polymer bound oxazaborolidine **(27)** on borane reduction of an imine.

Irrespective of the amount of polymer supported oxazaborolidine **(27)** or the reductant used, only the uncatalysed reduction was observed. The polymer used here is polyacrylamide and the solvent for the reaction is THF. Usually when polymer-based reagents are used in a reaction, the solvent is chosen that will swell the polymer giving accessibility to the supported reagent. This may be one reason why the polymer supported oxazaborolidine **(27)** did not work. If the oxazaborolidine was inaccessible then the imine would not be able to complex to it and therefore only the uncatalysed reduction would occur. This could be tested by using a more non polar solvent, which should swell the polymer better. Obviously the effect of the non polar solvent, on the solution phase reaction, would also have to be investigated. One other factor is that the exact loading for this oxazaborolidine is uncertain as already discussed in chapter 2.

5.2.4.3.2 Effect of MCM-41 supported oxazaborolidines **(32)** and silica supported oxazaborolidine **(33)** on borane reduction of an imine.

In this case, MCM-41 supported oxazaborolidine **(32)** and silica supported oxazaborolidine **(33)** gave the same results. Only the 0.1 equivalents of supported oxazaborolidine could be assessed. This gave the racemic product but this is probably due to the support and not the inaccessibility of the oxazaborolidine. It has already been shown that MCM-41 **(1)** (or silica) alone has a detrimental effect on the solution phase reduction. One method that could be used to test and or prevent this effect would be to cap the silicate surface. It is possible that after the boronic acid has been supported, the rest of the silicate surface can be deactivated by the addition of

chlorotrimethylsilane. This is very reactive and small and created an organic "coat" to the walls of MCM-41 **(1)** (or silica).

When 1 equivalent supported oxazaborolidine was tested then the HPLC trace could not be interpreted. Other side reactions were occurring and instead of getting two sharp peaks in the region where the amine enantiomers come, there were three very broad peaks. There was no way of knowing which of these peaks if any were the amine and therefore the reaction could not be followed **(Figure 37)**.

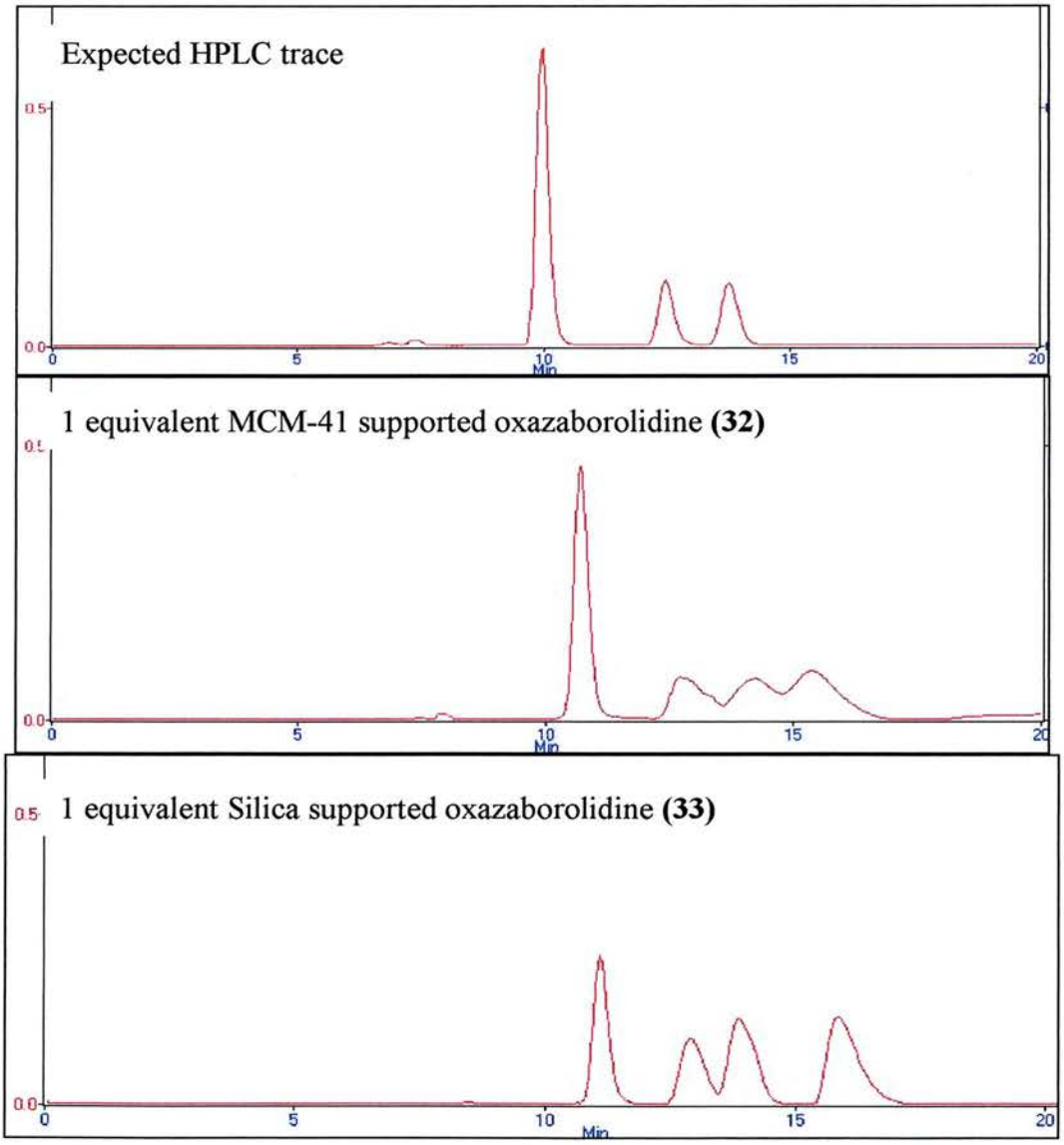


Figure 37 – HPLC traces from the 1 equivalents MCM-41 supported oxazaborolidine (32) and silica supported oxazaborolidine (33) imine reduction.

As the reduction is followed by HPLC the species present in the mixture are unknown. One possibility is that the silicate is decomposing the imine. To check this, the imine **(52)** was dissolved in THF and MCM-41 **(1)** (or silica) was added. The imine **(52)** did slowly degrade and one of the products that can be seen by HPLC is in the region of the amine **(54)**. This does not account of all the HPLC peaks seen in the traces above. What is exactly going on in this reaction is unknown and is only seen with this amount of silicate supported oxazaborolidine. Another possibility is that the imine **(52)** is reacting with the amine **(54)**, but again there is no proof of this.

5.2.4.3.3 Effect of changing the order of addition for the 0.1 equivalents MCM-41 supported oxazaborolidine **(32)** catalysed imine reduction.

Although changing the order of addition of reagents in the solution phase was detrimental it was still investigated with respect to the MCM-41 supported oxazaborolidine **(32)**. This was because there is a positive point to adding the MCM-41 supported oxazaborolidine **(32)** and borane first and then adding the imine **(52)**, the imine would be in contact with the MCM-41 for the least possible time. However, when this was tested using 0.1 equivalents MCM-41 supported oxazaborolidine **(32)** only the uncatalysed reaction was observed probably for the same reasons as for the solution phase reaction.

5.2.5 Asymmetric reductions of Acetophenone.

The same reactions and conditions that were run for imine **(52)** have also been run for acetophenone. However, it will be shown that the acetophenone system acts very differently to the imine system and in general is well behaved.

5.2.5.1 Investigation into solution phase asymmetric ketone reduction.

Table 27 shows the results for the solution phase investigation into oxazaborolidine catalysed reduction of acetophenone.

Reductant[a]	Catalyst[b]	e.e./ % (Config.)[c]	Conv./ %
BTHF	None	0	40
CB		0	0
BDMS		0	97
BTHF	A	> 99 (R)	> 99
CB		~ 90 (R) [d]	~ 80 [d]
BDMS		> 99 (R)	97
BTHF		78 (R) [e]	40
BTHF		94 (R) [f]	36
BTHF	B	68 (R)	11
CB		67 (R)	2
BDMS		> 99 (R)	92
BTHF	A[g]	41 (R)	50
CB		54 (R)	8
BDMS		88 (R)	91

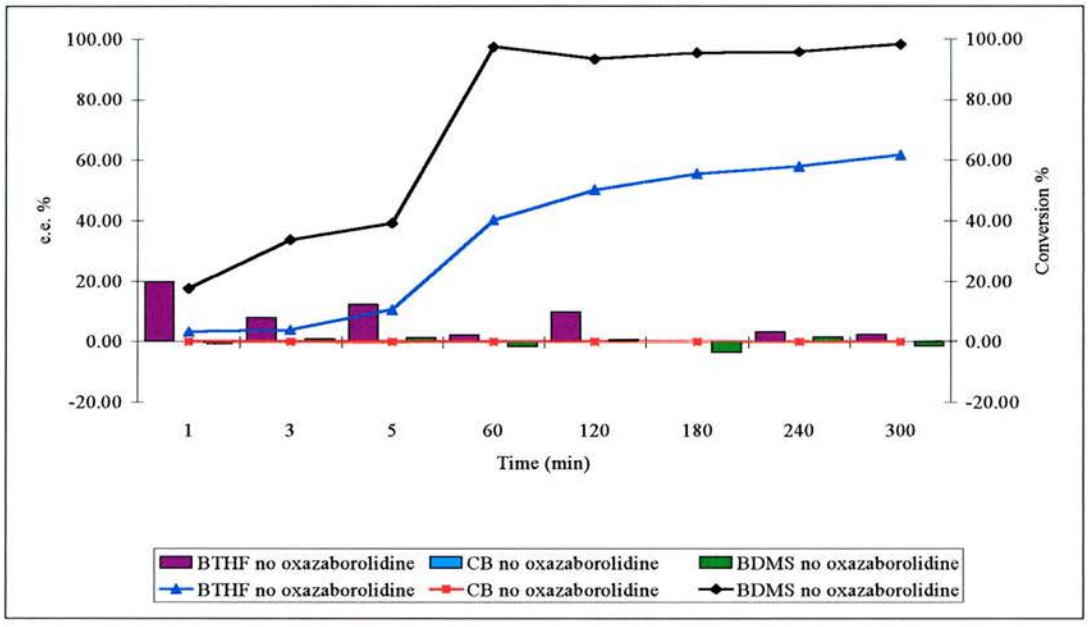
[a]BTHF = Borane THF adduct, CB = Catecholborane, BDMS = Borane DMS adduct. [b]A = (S) methyl CBS oxazaborolidine, B = (S) phenyl oxazaborolidine, [c]from comparison with optical rotation.[31] [d] The data point at 60 min contained an error - see section 5.2.5.1.3, [e]Run at 0 °C – See Fig 38, [f] Run at –78 °C, [g] Order of addition changed - see section 5.2.5.1.5.

Table 27 – Solution Phase Acetophenone Reductions after 1 hour.

5.2.5.1.1 Effect of no oxazaborolidine.

As expected, all the products are racemates irrespective of reducing agent. However, the different reducing agents do give different conversions; catecholborane gave no conversion and borane DMS was the most active. Borane THF and borane DMS do reduce acetophenone in the absence of oxazaborolidine but there is a long enough

delay so that when oxazaborolidine is present, the background uncatalysed reaction will not interfere, especially in the case of borane THF and Catecholborane **(Chart 2)**. In the literature the asymmetric reduction of acetophenone is over in 5 min.[4]



e.e. = bars, conversions = lines.

Chart 2 – Effect of no oxazaborolidine on the borane reduction of acetophenone.

5.2.5.1.2 Effect of temperature.

Acetophenone was reduced, in the presence of (S) methyl CBS oxazaborolidine, using borane THF as the reductant at various temperatures. The reductions were followed by HPLC at room temperature, 0 °C or at - 78 °C.

The acetophenone system behaves more as expected, the conversion and e.e. is lowered as the temperature is reduced. However from table 27, 0 °C gave lower e.e. than - 78 °C. At 0 °C there are unidentified side reactions occurring which are not seen at room temperature or - 78 °C. This can been seen by many more peaks on the HPLC trace; probably one of the side products comes at the same place as one enantiomer of the alcohol and therefore lowers the e.e. **(Figure 36)**. As this is an

analytical HPLC column then there is not sufficient material to collect and identify unless a mass spectrometer was attached, which was not available. (One run has a total of 0.02 mg injected). The optical rotation of the amine **(54)** is small, so it cannot be used accurately to determine the e.e. either.

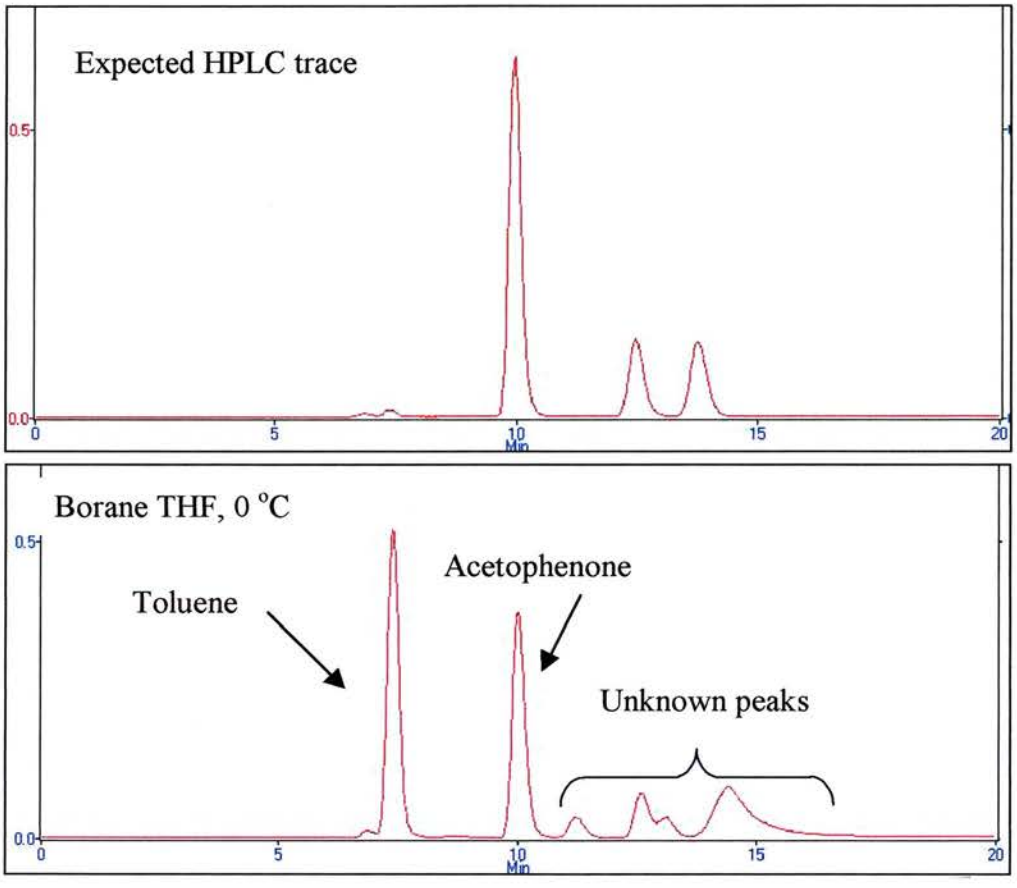


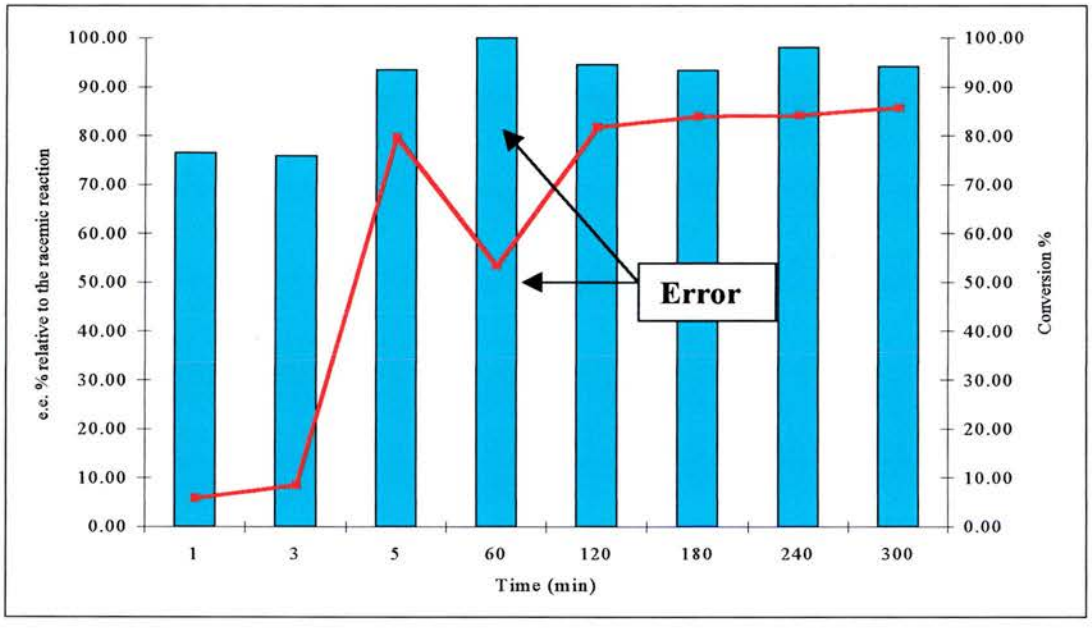
Figure 38 – HPLC trace for acetophenone asymmetric reduction at 0 °C with borane THF.

5.2.5.1.3 Effect of reducing agent.

All the reductants gave excellent yields and e.e.'s after 60 mins, as shown in table 27. In fact, these e.e.'s and conversions had been reached after 5 mins and previous to this the e.e.'s had been about 75% with the conversions rising rapidly. The results here are very good, as the uncatalysed borane reduction is not significant, especially for catecholborane and borane THF. Even with borane DMS, which seems to be the most active in the absence of oxazaborolidine. The conversion after 5 min was 39 %.

However, when oxazaborolidine is present the uncatalysed borane reduction seems to have little effect.

The only problem was that during the catecholborane reaction the HPLC sample taken after 60 min did not run properly down the HPLC so the actual e.e.'s obtained was 100 % and conversion 53 %. However, the e.e.'s at 5 min and 120 min were 93 and 95 % respectively and the conversions were 80 and 82 % respectively **(Chart 3)**.



e.e. = bars, conversions = lines.

Chart 3 – Effect of Catecholborane on Asymmetric Reduction of Acetophenone.

Therefore, irrespective of the reducing agent used the asymmetric reaction is over after 5 min. With borane DMS the reaction seems to be near completion after 1 min and with catecholborane and borane THF the asymmetric reaction has a small latent period of 3 min and then the reaction occurs very rapidly until after 5 min it is complete. The difference between borane DMS and borane THF is unclear as already discussed.

5.2.5.1.4 Effect of (S) phenyl oxazaborolidine.

(S) Phenyl oxazaborolidine was prepared as described in section 5.2.4.1.4. (S) Phenyl oxazaborolidine does reduce acetophenone asymmetrically to some extent with all the borane reductants. Interestingly, with borane THF and Catecholborane the conversions were very low and the e.e. was only around 70 %. However, borane DMS, as with all the experiments already discussed, is more active and gives excellent e.e. and conversions after 60 mins. This looks promising for the solid supported oxazaborolidines, as this hindered oxazaborolidine is active with borane DMS. Therefore, if the solid supported oxazaborolidines are not active it will not be due to steric bulk but for some other reason.

5.2.5.1.5 Effect of changing the order of addition.

Changing the order of addition should not be so important for acetophenone compared to the imine reduction as the uncatalysed reaction in the case of acetophenone is much slower. However, when this was investigated although the reduction was asymmetric the e.e.'s were not as good and the conversions were lower. For the asymmetric reduction of acetophenone, better results are obtained if the acetophenone and oxazaborolidine were pre - mixed and then the borane added. Altering the order of addition shifts the equilibria in this process, which has the effect of lowering the conversion and e.e.

5.2.5.2 Investigation into the effect of silicates on the solution phase asymmetric ketone reduction.

Table 28 shows the effect of added silicates in the solution phase reduction of acetophenone.

Reductant[a]	Other conditions	e.e./ % (Config.)[b]	Conv./ %
BTHF	No silicate added	> 99 (R)	> 99
CB		~ 90 (R)	~ 80
BDMS		> 99 (R)	97
BTHF	Molecular sieves	71 (R)	28
CB		48 (R)	38
BDMS		83 (R)	> 99
BTHF	20 mg MCM-41 **(1)**	42 (R)	13
CB		33 (R)	8
BDMS		47 (R)	80
BTHF	200 mg MCM-41 **(1)**	43 (R)	8
CB		19 (R)	8
BDMS		4 (S)	53
BTHF	50 mg Silica	1 (S)	7
CB		1 (S)	20
BDMS		1 (R)	89
BTHF	500 mg Silica	23 (R)	19
CB		10 (R)	16
BDMS		1 (R)	75
BTHF	MCM-41supported boronic acid **(30)**	89 (R)	47
CB		48 (R)	7
BDMS		83 (R)	99
BTHF	Silica supported boronic acid **(31)**	91 (R)	43
CB		95 (R)	28
BDMS		79 (R)	98

[a]BTHF = Borane THF adduct, CB = Catecholborane, BDMS = Borane DMS adduct. [b]from comparison with optical rotation.[31]

Table 28 – Effect Of Silicates On The Solution Phase Asymmetric Acetophenone Reduction After 1 Hour.

5.2.5.2.1 Effect of molecular sieves on the solution phase ketone reduction

The use of 4 Å powered molecular sieves did not prevent the asymmetric reaction as with the imine reduction however, the e.e.'s and conversions are lower. Again, borane DMS gave the best results but even in this case in the presence of molecular sieves, the e.e. is 87 % compared to > 99 % without molecular sieves. The effect is even more marked with borane THF where the e.e. is 71 % compared to > 99 % and the conversion is only 28 % in the presence of molecular sieves compared to > 99% without. With Catecholborane the e.e.'s are the lowest and the conversion is not much better than with borane THF.

At best, there would be no effect of molecular sieves as the solution phase reductions give excellent results and it would be difficult to improve these. This is the same for all the silicates tested - any effect can only be detrimental.

5.2.5.2.2 Effect of MCM-41 **(1)** on the solution phase asymmetric ketone reduction.

20 mg of MCM-41 **(1)** gives better results than with 200 mg MCM-41 **(1)** but both conditions are unfavourable for the solution phase asymmetric reduction.

When there is only 20 mg of MCM-41, borane THF and borane DMS give similar e.e., 42 % and 47 %, respectively. However the conversions are very different, 13 % and 80 % respectively. This again shows how borane DMS is more active than borane THF but this is not at the expense of the enantioselectivity. Catecholborane gives the worse e.e. and conversion and there is hardly any activity. When an MCM-41 **(1)** slurry is used then borane THF still gives the same e.e. but the conversion has

dropped to 8 %. Borane DMS gives approximately 53 % conversion but only the racemic product is obtained.

From the results it can be reasonably assumed that MCM-41 **(1)** is actually decomposing the borane as the conversions are lower than the uncatalysed reaction, except in the case of catecholborane, but the conversions are so low they are in the ± 5 % error already discussed. Therefore, the MCM-41 **(1)** is not just interfering with the asymmetric reduction but with the uncatalysed reduction as well. This is backed up by the fact that when the borane (especially borane DMS) was added, there was a large amount of gas evolved that was not observed in the solution phase reductions. This would also explain why borane DMS was not the best reductant, as if borane DMS was decomposed the fastest, it would not be available for the reduction. The low conversions were not observed with the imine reductions, probably because the uncatalysed reaction was so fast, that the borane was used up before it had time to decompose.

5.2.5.2.3 Effect of silica on the solution phase asymmetric ketone reduction.

The effects of silica observed are the same as for the MCM-41 **(1)** experiments but the effect is greater. The observed amount of gas evolved was also greater. It appears that although MCM-41 **(1)** has a larger surface area, silica decomposes borane faster. The observed conversions are virtually unchanged after 1 min of the addition of the borane. For borane THF and catecholborane the conversions are approximately 20 %, in the case of silica slurry with borane DMS a conversion 75 % was obtained. An e.e. of 23 % was obtained using borane THF and the other boranes gave racemates.

5.2.5.2.4 Effect of MCM-41 or silica supported boronic acid **(30 and 31)** on the solution phase asymmetric ketone reduction.

As the silicate supported oxazaborolidines that have been prepared still have some of the free boronic acid the effect of these was examined. Therefore, the silicate supported boronic acids **(30 and 31)** were added to the solution phase asymmetric reductions. To examine their effect the same equivalents of silicate supported boronic acid as (S) methyl CBS oxazaborolidine were used. Apart from borane DMS, all the conversions are very much lower compared to the solution phase reductions, irrespective of whether the support is MCM-41 or silica. With silica supported boronic acid **(31)** the e.e.'s are better than with MCM-41 supported boronic acid **(30)**. This effect is small except for the catecholborane reduction, and the effect here is greater; i.e. 95 % e.e. compared to 48 %; however, the cause of this is not known. The e.e.'s on the whole are good but not as high as the solution phase reductions. The effect observed here is probably due to the support, rather than the presence of the boronic acid.

This result is promising for the solid supported oxazaborolidine because it proves that in the presence of this amount of silicate the asymmetric reaction will take place. The next thing to investigate is whether the solid supported oxazaborolidines will catalyse the reduction of acetophenone, or whether only the uncatalysed reduction will take place.

5.2.5.3 Effect of Solid supported oxazaborolidines on asymmetric ketone reduction.

From the previous work it looked hopeful that some enantioselectivity would be observed. The table below shows the results obtained.

Reductant[a]	Catalyst[b]	e.e./ % (Config.)[c]	Conv./ %
BTHF	Homogeneous reduction	> 99 (R)	> 99
CB		~ 90 (R)	~ 80
BDMS		> 99 (R)	97
BTHF	0.1 equivalents A	2 (R)	17
CB		13 (S)	6
BDMS		3 (R)	97
BTHF	1 equivalent A	3 (S)	32
CB		1 (R)	8
BDMS		0	85
BTHF	0.1 equivalents B	2 (S)	17
CB		7 (R)	2
BDMS		31 (R)	98
BTHF	1 equivalent B	40 (R)	8
CB		28 (R)	12
BDMS		29 (R)	94
BTHF	0.1 equivalents C	4 (R)	11
CB		3 (S)	5
BDMS		29 (R)	99
BTHF	1 equivalent C	18 (R)	15
CB		21 (R)	9
BDMS		22 (R)	82
BTHF	0.1 equivalents B[d]	25 (R)	14
CB		20 (R)	11
BDMS		51 (R)	82

[a]BTHF = Borane THF adduct, CB = Catecholborane, BDMS = Borane DMS adduct. [b] A = polyacrylamide supported oxazaborolidine **(27)**, B = MCM-41 supported oxazaborolidine **(32)**, C = silica supported oxazaborolidine **(33)** [c]from comparison with optical rotation.[31] [d]Change in order of addition – see section 5.2.5.3.3.

Table 28 – Effect of Solid Supported Oxazaborolidines on the Asymmetric Acetophenone Reduction after 1 Hour.

5.2.5.3.1 Effect of polymer bound oxazaborolidine **(27)** on borane reduction of acetophenone.

As for the imine reduction, the polyacrylamide supported oxazaborolidine is completely inactive and only the uncatalysed reaction occurs. For some reason the ketone is not complexing to the oxazaborolidine, probably due to inaccessibility of the oxazaborolidine. The most likely reason, as in the imine reductions, is the amount by which the polymer swells.

5.2.5.3.2 Effect of MCM-41 supported oxazaborolidines **(32)** and silica supported oxazaborolidine **(33)** on borane reduction of acetophenone.

Unlike the imine reduction, acetophenone will reduce enantioselectivity in the presence of MCM-41 or silica supported oxazaborolidine. The e.e.'s are low, but these are promising results for further development.

In the presence of 0.1 equivalents MCM-41 supported oxazaborolidine **(32)** only borane DMS gives any enantioselectivity (e.e. = 31 %) with an excellent conversion. If the amount of oxazaborolidine is increased then all the reductants give some enantioselectivity (borane THF 40 %, Catecholborane 28 %, borane DMS 29 %). However, borane DMS is the only one which gives a good conversion (94 %), with borane THF and Catecholborane the conversion is only 8 % and 12 % respectively. Silica supported oxazaborolidine **(33)** gives the similar results within experimental error.

5.2.5.3.3 Effect of changing the order of addition for 0.1 equivalents MCM-41 supported oxazaborolidine **(32)** reduction of acetophenone.

Although, in the solution phase changing the order of addition lowered the e.e., when the order was changed using 0.1 MCM-41 supported oxazaborolidine **(32)** the e.e.'s were improved. Instead of obtaining a racemate when borane THF and Catecholborane were used e.e.'s of 25 % and 20 % respectively were obtained. However, the conversions are very low. The most promising and exciting result was from using borane DMS as the reductant. After 1 hour a 51 % e.e. and an 82 % conversion was obtained. Due to time constraints this has not been taken any further, but subsequent experiments could include testing 1 equivalent MCM-41 supported oxazaborolidine **(32)** and silica supported oxazaborolidine **(33)**.

5.2.6 Differences Between Oxazaborolidine Catalysed Asymmetric Reduction of Imine (52) and Acetophenone.

In general, acetophenone reductions are better behaved than imine **(52)** reductions. The differences between imine and ketone reductions can be rationalised in terms of the relative affinity of nitrogen or oxygen for boron. Nitrogen has a greater affinity for boron than oxygen, this will mean that the imine **(52)** will co-ordinate to the borane much more readily than the acetophenone will. Therefore, in the uncatalysed reaction, the reduction of the imine **(52)** will occur more readily than the acetophenone reduction (as the borane must complex to the substrate to reduce it).

The asymmetric reaction is more complex. For the oxazaborolidine to have an effect on the reduction the borane must complex to the nitrogen of the oxazaborolidine and the substrate to the boron of the oxazaborolidine. In the case of acetophenone this is more favoured than the complexation to just borane. This is because in the

uncatalysed reaction oxygen complexes to boron, in the asymmetric reaction borane complexes to nitrogen. However, in the case of the imine irrespective of whether the uncatalysed or catalysed asymmetric reaction is taking place the borane complexes to a nitrogen. This will reduce the favourability of forming the oxazaborolidine complex **(Figure 37)**.

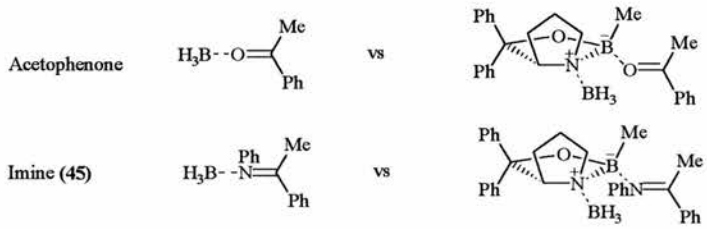


Figure 37 – Complexes for the Uncatalysed and Asymmetric Catalysed Reduction of Acetophenone and Imine (52).

The other reason that acetophenone gives better results is that it is less hindered. The oxazaborolidine complexes to the oxygen of the ketone whereas in the analogous system of the imine, it complexes to the nitrogen. However, in the case of the nitrogen there is another bulky group on the nitrogen, which due to steric hindrance will make the complexation less favourable. However, from the results where there is no oxazaborolidine present, it can be presumed that borane has a greater affinity for nitrogen than oxygen due to the rates of the uncatalysed reductions. As with everything else in this system, it is a matter of balance. If the correct balance is obtained then the reduction will be enantioselective.

The tables below show the conditions that give an e.e. greater than 40 % and conversion greater than 30 % in 1 hour.

Imine **(52)**:

	Borane[a]	**Catalyst**	**e.e. %/ (Config.)**	**Conversion (%)**
Solution phase	BTHF	A	69 (R)	87
	CB	A	47 (S)	98
	CB	B	49 (R)	91
	BTHF	C	81 (R)	30

[a] BTHF = Borane THF, CB = catecholborane, [b] A = (S) methyl CBS oxazaborolidine, B = (R) methyl CBS oxazaborolidine, C = (S) phenyl oxazaborolidine.

Acetophenone:

	Borane[a]	**Catalyst**[b]	**e.e. %/ (Config.)**	**Conversion (%)**
Solution phase	BTHF	A	> 99 (R)	> 99
	CB	A	~ 90 (R)	~ 80
	BDMS	A	> 99 (R)	97
	BTHF	A[c]	78 (R)	40
	BTHF	A[d]	94 (R)	36
	BDMS	B	> 99 (R)	92
	BTHF	A[e]	41 (R)	50
	BDMS	A[e]	88 (R)	91
Added silicate to solution phase reduction	CB	C	48 (R)	38
	BDMS	C	83 (R)	> 99
	BDMS	D	47 (R)	80
	BTHF	E	89 (R)	47
	BDMS	E	83 (R)	99
	BTHF	F	91 (R)	43
	BDMS	F	79 (R)	98
Solid phase	BDMS	G[e]	51 (R)	82

[a] BTHF = Borane THF, CB = catecholborane, BDMS = Borane DMS, [b] A = (S) methyl CBS oxazaborolidine, B = (S) phenyl oxazaborolidine, C = (S) methyl CBS oxazaborolidines/ molecular sieves, D = (S) methyl CBS oxazaborolidine/ 20 mg MCM-41 **(1)**, E = (S) methyl CBS oxazaborolidine/ MCM-41 supported boronic acid **(30)**, F = (S) methyl CBS oxazaborolidine/ Silica supported boronic acid **(31)**, G = 0.1 equivalents MCM-41 supported oxazaborolidine **(32)**, [c] at 0 °C, [d] at – 78 °C, [e] Change in order of addition.

Table 30 – Conditions That Reduce Imine (52) And Acetophenone With An e.e. Greater Than 40 % And Conversion Greater Then 30 % In 1 Hour.

5.2.6 Conclusions.

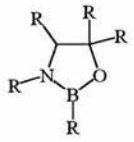
- The imine system is more complicated than the corresponding ketone system.
- Oxazaborolidine catalysed asymmetric reductions of imine **(52)** are problematic and it is difficult to get high enantioselectivities.
- Oxazaborolidine catalysed asymmetric reduction of acetophenone gives good e.e. and conversions in solution.
- Slightly altering the reaction conditions can have a dramatic effect on the enantioselectivity and conversions of the asymmetric reaction.
- Different boranes give different e.e. and conversions.
- In the case of imine **(52)** reduction, enantioselectivity depends on borane and oxazaborolidine. For acetophenone reductions enantioselectivity is only dependent on oxazaborolidine.

5.2.7 Future Work.

There are a large number of different investigations that can come out of this work. Below are listed some possible investigations that could be undertaken for both the imine and ketone reduction.

1. Solution Phase:

- Investigation into the effect of different concentrations of reagents.
- Effect of different oxazaborolidines; examine the effect of changing the size of the group on boron, the group on nitrogen and on the aromatic rings **(Figure 38)**.



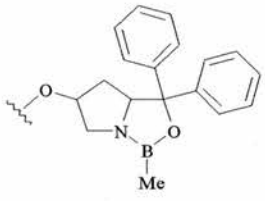
R = groups that can be varied.

Figure 38 – General Oxazaborolidine Structures and the Groups that could be varied.

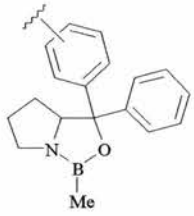
- Effect of changing the size of the two groups around the carbonyl or C=N bond in the substrate.

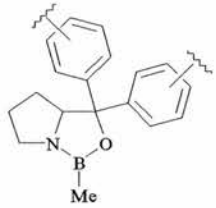
2. Solid Supported Oxazaborolidines.

- Investigate the effect of silicate supported oxazaborolidines with different orders of addition of reagents.
- Investigate effect of "capping" surface of silicate supported oxazaborolidines.
- Investigate effect of different equivalents of solid supported oxazaborolidines.
- Investigate different solid supported oxazaborolidines prepared from different amino alcohols. e.g. see structures below.



Tether to support via hydroxyl group in the oxazaborolidine derived from hydroxy proline.





Tether to support through one or both phenyl rings on the oxazaborolidine.

5.3 Experimental

As for Chapter 2

5.3.1 HPLC Systems.

5.3.1.1 HPLC System for GSK Imine ***(51)****/ GSK Amine* ***(53)****.*

HPLC machine – Gilson 305

HPLC Column - Prodigy 5μ ODS 2, 150 x 4.6 mm supplied from Phenomenex.

Sample size - 20 μl of a 0.25 mg ml^{-1} solution

Flow Rate – 1 ml min^{-1}.

UV detector - 215 nm.

Solvent System:

Time / min	**Aqueous phase % Water : Acetonitrile 95 : 5 + 0.1 % TFA**	**Organic Phase % Water : Acetonitrile 5 : 95**
0	85 %	15 %
15	62.5 %	37.5 %
28	62.5 %	37.5 %
30	85 %	15 %

Table 16 - Solvent System for HPLC

5.3.1.2 HPLC System for Imine ***(52)*** *And Acetophenone.*

HPLC machine - BioCad Sprint Perfusion Chromatography System.

HPLC Column - Chiralcel OD-H, 250 x 4.6 mm supplied from Diacel Chemical Industries Ltd.

Sample size - 20 μl of a 1 mg ml^{-1} solution

Flow rate – 0.5 ml min^{-1}.

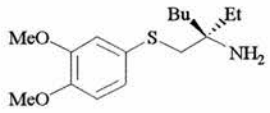
UV detector - 215 nm and 254 nm.

Solvent System - 5 % Ethanol in Heptane

5.3.2 Synthesis of Imine Substrates.

5.3.2.1 Preparation of (3S)-3-butyl-3ethyl-7,8-dimethoxy-5-phenyl-2,3-dihydro-1,4-benzothiazepine (GSK Imine) **(51)**.

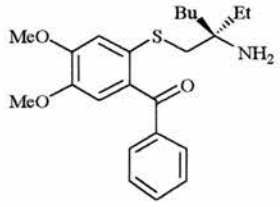
(3R)-3-{[(3,4-dimethoxyphenyl)sulfanyl]methyl}heptan-3-amine (amino sulfide) **(49)**



The title compound was synthesised by a procedure developed by GlaxoSmithKline. In deionised water (15 ml), the (2 R)-2-ammonio-2-ethylhexyl sulphate (5.04 g, 22 mmol) and 3,4-dimethoxythiophenol (4 g, 23 mmol in THF 30 ml) were added under nitrogen. Sodium hydroxide (24 % w/w, 12 ml) were added dropwise over 45 min. The mixture was stirred overnight at room temperature and then refluxed for 3 hours at 98 °C. More (2 R)-2-ammonio-2-ethylhexyl sulphate (5.04 g, 22 mmol) was added followed by sodium hydroxide (24 % w/w, 12 ml) was added dropwise over 90 min. The mixture was refluxed for 2 hours at 98 °C, once the mixture was cooled ether (30 ml) was added and the layers separated. The product was extracted with ether and the organic layers washed with brine (30 ml), citric acid (1 M, 100 ml), brine (50 ml). The product was in the citric acid phase so this was neutralised with sodium bicarbonate and the product was extracted into DCM. The solvent was removed to give the *title compound* **(49)** as a colourless oil (1.7 g, 25 %); δ_H ($CDCl_3$) 0.84 (3 H, t, *J* 7, CH_2CH_3), 0.85 (3 H, t, *J* 7, CH_2CH_3), 1.20 (4 H, m, CH_2CH_2Me and CH_2CH_2Me), 1.53 (4 H, m, 2 x CCH_2), 3.04 (2 H, s, SCH_2), 3.84 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 6.76 (1 H, d, *J* 6, Ar H-6), 7.05 (2 H, m, 2 x Ar CHS); δ_C ($CDCl_3$) 8.0, (Me), 13.0 (Me and CH_2), 21.0, 21.2, 24.8 (3 x CH_2), 53.5 (SCH_2), 56.0, 56.9 (2 x OMe), 111.8, 115.1, 124.6 (3 x CH Ar), 127.8 (SC quat.), 149.4, 149.9 (2 x MeOC quat.); ν_{max} (Thin Film) 3412 (NH_2), 2957 (CH), 2871 (OCH_3), 1584 (NH_2); m/z (CI+) 595 ($[2M+H]^+$), 339 ($[MH+MeCN]^+$), 298 (MH^+), 281

([MH-NH_3]$^+$), 169 ([$(MeO)_2PhS$]$^+$), 143 ([SCHBu(Et)]$^+$). Characterisation agrees with authentic samples prepared in the pilot plant at GlaxoSmithKline.

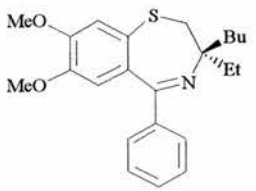
(2-{[(2R)-2-amino-2-ethylhexyl]sulfanyl}-4,5-dimethoxyphenyl)(phenyl)methanone (Amino benzophenone) **(50)**



The title compound was synthesised by a procedure developed by GlaxoSmithKline. In DCM (10 ml), amino sulfide **(49)** (1.65 g, 5.5 mmol) was added and the reaction cooled to 0 °C under nitrogen. Triflic acid (1 ml, 11 mmol) was added dropwise over 30 min, not allowing the temperature to rise above 10 °C. The mixture was allowed to warm to room temperature and benzoyl chloride (0.8 ml, 6.7 mmol) was added dropwise over 20 min and the reaction was refluxed overnight. After the reaction had cooled water (5 ml) was added and stirred for 30 min. The layers were separated and the organic phase was stirred with sodium hydroxide (2 M, 5 ml) for 20 min. The layers were separated and the organic phase washed with water (50 ml) and brine (50 ml) followed by the solvent being removed under reduced pressure to give the *title compound* **(50)** as a dark purple oil (2.0 g, 89 %); δ_H 0.74 (3 H, t, *J* 6, CH_2CH_3), 0.85 (3 H, t, *J* 8, CH_2CH_3), 1.19 (4 H, m, CH_2CH_2Me and CH_2CH_2Me), 1.41 (4 H, m, 2 x CCH_2), 2.96 (2 H, s, SCH_2), 3.96 (3 H, s, OCH_3), 4.11 (3 H, s, OCH_3), 6.91 (1 H, s, Ar CHS), 7.15 (1 H, s, Ar CHCOMe), 7.41 (1 H, t, *J* 7, m-CHPh), 7.74 (1 H, t; *J* 4, p-CHPh), 7.85 (1 H, d, *J* 7, o-CHPh) δ_C ($CDCl_3$) 8.5, 12.8 (2 x Me), 14.0, 20.1, 20.3, 22.9 (4 x CH_2), 53.4 (SCH_2), 55.4, 55.8 (2 x OMe), 108.3, 111.8 (2 x CH Ar), 127.5 (SC quat.), 128.4, 128.6, 130.0 (3 x CH Ph), 144.9, 145.3 (2 x MeOC quat.); ν_{max}

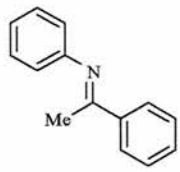
(Thin Film) 3364 (NH_2), 2958 (CH), 2871 (OCH_3), 1663 (CO),1594 (NH_2); m/z 402 (MH^+), 273 ($[(MeO)_2Ph\ (PhCO)S]^+$). Characterisation agrees with authentic samples prepared in the pilot plant at GlaxoSmithKline.

(3R)-3-butyl-3ethyl-7,8-dimethoxy-5-phenyl-2,3-dihydro-1,4-benzothiazepine (GSK Imine) **(51)**



The title compound was synthesised by a procedure developed by GlaxoSmithKline. In toluene (12 ml), amino benzophenone **(50)** (1.96 g, 4.88 mmol) and citric acid (0.14 g, 0.73 mmol) were added together and the mixture refluxed with a Dean-Stark apparatus under nitrogen for 5 hours. The reaction was cooled and washed with brine (2 x 30 ml). The product was purified by column chromatography (ethyl acetate: *i*-hexane 4:1) to give the *title compound* **(51)** as a yellow oil (1.0 g, 53 %); δ_H ($CDCl_3$) 0.87 (3 H, t, *J* 7, CH_2CH_3), 0.88 (3 H, t, *J* 7, CH_2CH_3), 1.26 (4 H, m, CH_2CH_2Me and CH_2CH_2Me), 1.60 (4 H, m, 2 x CCH_2), 3.25 (2 H, s, SCH_2), 3.68 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 6.67 (1 H, s, Ar CHS), 7.09 (1 H, s, Ar CHCOMe), 7.32 (2 H, m, p- and m-CHPh), 7.54 (1 H, m. o-CHPh); δ_C ($CDCl_3$) 8.3, 13.5 (2 x Me), 23.2, 26.5, 32.9, 39.3 (4 x CH_2), 49.7 (NC quat), 55.8 (2 x OMe), , 63.9 (SCH_2), 113.5, 14.8 (CH Ar), 127.7, 129.3, 129.4 (3 x CH Ph). 132.9 (SC quat.), 143.2 (C quat Ar), 148.4, 149.0 (2 x MeOC quat.), 160.0 (C=N), 163.8 (C quat. Ph); ν_{max} (Thin Film) 3064 (Aryl stretch), 2956, 2929, 2856 (CH stretch) 1745 (C=N stretch), 1618, 1593, 1565 (Aryl ring vibrations), 1257 (C-O-C stretch); m/z 384 (MH^+). Characterisation agrees with authentic samples prepared in the pilot plant at GlaxoSmithKline.

*5.3.2.2 Preparation of (1-Phenylethylidene)aniline (Imine)***(52)**.



The title compound was synthesised by a procedure reported by Cobas and co-workers.[32] In DCM (25 ml), acetophenone (8 mmol, 0.93 ml), aniline (9.6 mmol, 0.87 ml) and triethylamine (1.6ml) were added together and cooled in an ice bath under nitrogen. Titanium (IV) chloride (1 M, 5 mmol, 5 ml, in 5 ml DCM) was added dropwise and the mixture was stirred for half an hour at 0 °C. The mixture was then stirred at room temperature overnight. Saturated potassium carbonate solution (30 ml) was added and the mixture filtered. The organic phase was separated and washed with brine. The product was purified by column chromatography (ethyl acetate: hexane 10:1; The silica had first been neutralised by triethylamine), to give the *title compound* **(52)** as a yellow oil (1.4 g, 89 %); δ_H ($CDCl_3$) 2.26 (1 H, s, CH_3), 6.68 (10 H, m, 2 x Ph); δ_C ($CDCl_3$) 17.2 (CH_3), 119.4, 123.2, 127.2, 128.4, 129.0, 130.5 (2 x Ph), 139.6, 151.8 (2 x Ph quat.), 165.7 (C=N);ν_{max} (Thin Film) 3055, 3027 (CH stretch) 1636 (C=N stretch). NMR and IR agrees with Lit.[33]

5.3.3 General Procedures for Reduction Reactions

5.3.3.1 General Procedure Using Sodium Borohydride

The reduction was achieved by a modified procedure described by Cable and co-workers.[28] In DCM (3 ml), the imine (or acetophenone) (0.26 mmol) and glacial acetic acid (0.03 ml) were added together. The mixture was cooled to 0 °C and sodium borohydride (1.30 mmol) was added under nitrogen. The mixture was stirred for 10 minutes at 0 °C and more sodium borohydride (1.30 mmol) was added. The

reaction was allowed to warm to room temperature and was stirred until the reaction was complete. Hydrochloric acid (2 N, 4 ml) was added and the reaction stirred for 10 minutes. Water (2 ml) was then added, and the mixture was stirred for 15 minutes, and the layers are separated. The aqueous phase was back extracted with DCM (3 x 10 ml). The combined organic phases were added to saturated sodium hydrogen carbonate (10 ml) and stirred for 15 minutes and the layers separated. The organic phase was washed with water (10 ml) and dried over magnesium sulphate. The solvent was removed under reduced pressure to give the product.

5.3.3.2 General Procedure for Borane-Pyridine Reduction.

The reduction was achieved by a modified procedure described by Pelter and co-workers.[29] In ether (3 ml), the imine (or acetophenone) (0.26 mmol) and glacial acetic acid (1 ml) were added under nitrogen. To the solution, borane – pyridine adduct (1.56 mmol) was added dropwise. The reaction was stirred at room temperature until the reaction was complete. The reaction mixture was analysed by HPLC directly by dissolving a portion in the mobile phase.

5.3.3.3 General Procedure of Reduction of an Imine with Corey's Reagent and Borane – THF Complex.

The reduction was achieved by a modified procedure described by Cho and co-workers.[15] In THF (1.5 ml), The substrate (0.13 mmol) and (S)-methyl-CBS-oxazaborolidine (Corey's reagent) (1 M in toluene, 0.013 mmol) were added together and stirred for 10 min. Borane – THF (1 M, 0.15 mmol) was added dropwise under nitrogen. The reaction mixture was analysed by HPLC directly by dissolving a portion in the mobile phase.

5.3.3.4 General Procedure of Reduction of an Imine with Corey's Reagent and Catecholborane.

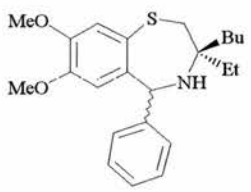
The reduction was achieved by a modified procedure described by Sakai and co-workers.[13] The procedure was the same as borane - THF reduction except catecholborane (1 M in toluene, 0.26 mmol) was used.

5.3.3.5 General Procedure of Reduction of An Imine With Corey's Reagent And Borane -DMS Complex.

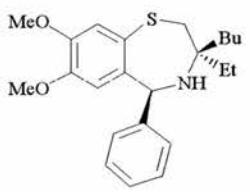
The reduction was achieved by a modified procedure described by Cho and co-workers.[15] The procedure was the same as borane -THF reduction except Borane - DMS (1 M, 0.15 mmol) was used.

5.3.4 Solution Reductions.

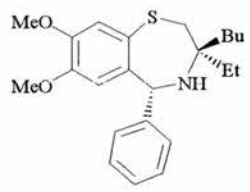
5.3.4.1 (3S) –3 –butyl –3 –ethyl -7,8 –dimethoxy –5 –phenyl -2,3 -tetrahydro-1,4-benzothiazepine (GSK amine) **(53)**



3R, 5R/S



3R, 5S



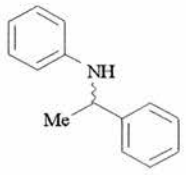
3R, 5R

Characterisation for 3R, 5R/S (Mixture of diastereoisomers 55:45).

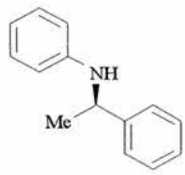
δ_H ($CDCl_3$) 0.89-1.08 (6 H, m, 2 x CH_2CH_3), 1.24-1.62 (4 H, m, CH_2CH_2Me and CH_2CH_2Me), 1.69-2.38 (4 H, m, 2 x CCH_2), 2.65-2.97 (2 H, m, SCH_2), 3.65 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 5.83 and 5.85 (1 H, 2 x s, CHPh) 6.63 (1 H, s, MeOCCH), 7.26 (1 H, s, CHCOMe), 7.38-7.62 (3 H, m, Ph); δ_C ($CDCl_3$) 6.4, 13.5 (2

x Me), 22.5, 24.4, 31.8, 39.5 (4 x CH_2), 40.1 (NC quat), 54.9, 55.2 (2 x OMe), 55.9 (CHN), 56.9 (SCH_2), 110.8, 115.0 (CH Ar), 125.9 (SC quat.), 127.2, 127.6, 127.9 (3 x CH Ph), 142.0 (C quat Ar), 143.3, 145.5 (2 x MeOC quat.), 147.1 (C quat. Ph); ν_{max} (Thin Film) 3322 (NH), 2957 (CH), 2871 (OCH_3); m/z 386 (MH^+), 274 ($SH(MeO)_2PhCH(Ph)NH^+$).

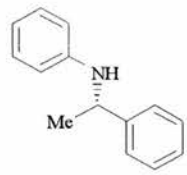
5.3.4.2 N-(1-Methylbenzyl)analine ***(54)***.



R,S amine



R amine

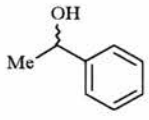


S imine

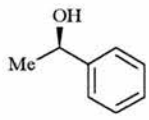
Characterisation for racemic amine **(54)**.

δ_H ($CDCl_3$) 1.52 (3 H, d, *J* 6, CH_3), 4.01 (1 H, br s, NH), 4.48 (1 H, q, *J* 7, CH), 6.51 - 7.40 (10 H, m, 2 x Ph); δ_C ($CDCl_3$) 24.9 (CH_3), 53.4 (CH_2), 113.3, 117.3, 125.9, 126.9, 128.7, 129.2 (2 x Ph), 145.3, 147.4 (2 x C quat.); ν_{max} (Thin Film) 3410 (NH), 2966 (CH). NMR agrees with Lit.[34]

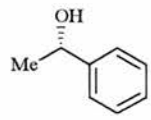
5.3.4.3 1-Phenylethanol ***(55)***.



R,S alcohol



R alcohol



S alcohol

Characterisation for racemic 1-phenyl ethanol **(55)**

δ_H ($CDCl_3$) 1.47 (3 H, d, *J* 7, CH_3), 2.39 (1 H, br s, OH), 4.86 (1 H, q, *J*, 7, CH), 7.28 – 7.36 (5 H, m, Ph); δ_C ($CDCl_3$) 24.4 (CH_3), 69.6 (CH), 124.8, 126.8, 127.9 (Ph), 145.4 (C quat.); ν_{max} (Thin Film) 3380 (0H), 2954 (CH). NMR agrees with Lit.[35]

5.4 References

1 S. Itsuno, K. Ito, A. Hirao and S. Nakahama, *J. Chem. Soc., Chem. Commun.*, 1983, 469.

2 S. Itsuno, K. Ito, A. Hirao and S. Nakahama, *J. Org. Chem.*, 1984, **49**, 555.

3 S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao and S. Nakahama, *J. Chem. Soc., Perkin Trans. 1.*, 1985, 2039.

4 E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551.

5 E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925.

6 E. J. Corey and C. J. Helal, *Angew. Chem. Int. Ed.*, 1998, **37**, 1987.

7 A. W. Douglas, D. M. Tschaen, R. A. Reamer and Y. -J. Shi. *Tetrahedron: Asymmetry*, 1996, **7**, 1303.

8 This crystal structure can be observed on the chemical database service at Daresbury http://cds3.dl.ac.uk/cds/cds.html

9 The United Kingdom Chemical Database Service, D. A. Fletcher, R. F. McMeeking and D. Parkin, *J. Chem. Inf. Comput. Sci.* 1996, **36**, 746.

10 K. Manju and S. Trehan, *Tetrahedron: Asymmetry*, 1998, **9**, 3365.

11 E. J. Corey and R. K. Bakshi, *Tetrahedron Lett.*, 1990, **31**, 611.

12 S. Jones and J. C. C. Atherton, *Tetrahedron: Asymmetry*, 2000, **11**, 4543.

13 T. Sakai, F. Y. Yan, S. Kashino and K. Uneyama, *Tetrahedron*, 1996, **52**, 233.

14 T. Sakai, F. Yan and K. Uneyama, *Synlett*, 1995,753.

15 B. T. Cho and Y. S. Chun, *J. Chem. Soc., Perkin Trans. 1.*, 1990, 3200.

16 B. T. Cho, M. H. Ryu, Y. S. Chun, C. Dauelsburg, S. Wallbaum and J. Martens, *Bull. Korean, Chem. Soc.*, 1994, **15**, 53.

17 B. T. Cho and Y. S. Chun, *Tetrahedron: Asymmetry*, 1992, **3**, 337.

18 C. Caze, *React. Func. Polym.*, 1995, **26**, 85.

19 C. Schunicht, A. Biffis and G. Wulff, *Tetrahedron*, 2000, **56**, 1693.

20 G. Giffels, J. Beliczey, M. Felder and U. Kragl, *Tetrahedron: Asymmetry*, 1998, **9**, 691.

21 N. El Moualij and C. Caze, *Eur. Polym. J.*, 1995, **31**, 193.

22 S. Itsuno, T. Matsumoto, D. Sato and T. Inoue, *J. Org. Chem.*, 2000, **65**, 5879.

23 S. Itsuno, M. Nakano, K. Ito, A. Hirao, M. Owa, N. Kanda and S. Nakahama, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2615.

24 S. Itsuno, K. Ito, A. Hirao and S. Nakahama, *J. Chem. Soc., Perkin Trans. 1.*, 1984, 2887.

25 K. Molvinger, M. Lopez and J. Court, *Tetrahedron Lett.*, 1999, **40**, 8375.

26 M. Felder, G. Giffels and C. Wandrey, *Tetrahedron: Asymmetry*, 1997, **8**, 1975.

27 M. Periasamy, G. Srinivas and P. Bharathi, *J. Org. Chem.*, 1999, **64**, 4204.

28 K. M. Cable, G. N. Wells and D. R. Sutherland, *J. Labelled Cpd. Radiopharm.*, 2000, **43**, 29.

29 A. Pelter, R. M. Rosser and S. Mills, *J. Chem. Soc., Perkin Trans. 1*, 1984, 717.

30 T. Morimoto, N. Nakajima and K. Achiwa, *Tetrahedron: Asymmetry*, 1995, **6**, 23.

31 K. Nakamura, Y. Inoue, T. Matsuda and I. Misawa, *J. Chem. Soc., Perkin Trans 1*, 1999, 2397

32 A. Cobas, E. Guitain and L. Castedo, *J. Org. Chem.*, 1993, **58**, 3113.

33 P. Nongkunsarn and C. A. Ramsden, *Tetrahedron*, 1997, **53**, 3805.

34 B. C. Ranu, A. Majee and A. Sarkar, *J. Org. Chem.*, 1998, **63**, 370.

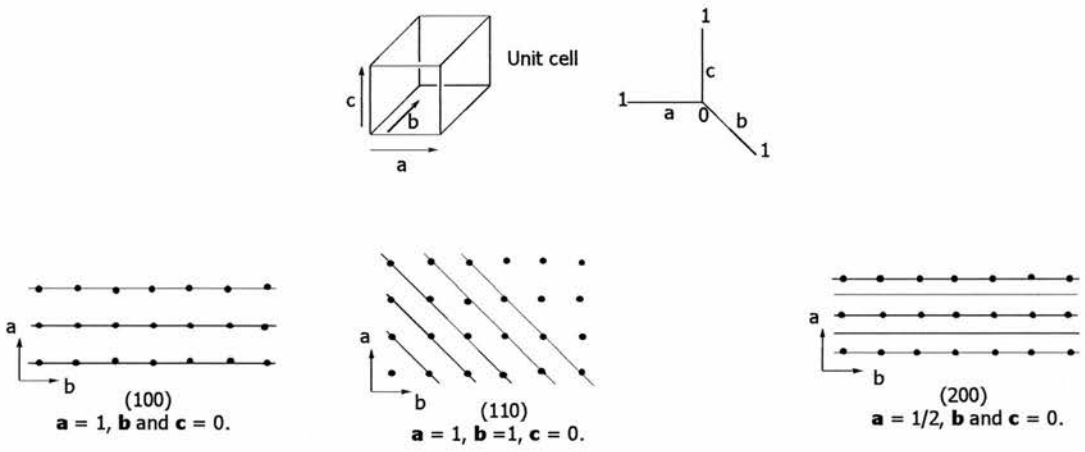
35 Y. Kita, Y. Takebe, K. Murata, T. Naka and S. Akai, *J. Org. Chem.*, 2000, **65**, 83.

Chapter 6

Appendix

6.1 Miller Planes.

These materials are routinely characterised by powder X-ray diffraction (XRD), which confirms the spacing of the Miller planes[1] and is used as a fingerprint for the phase. X-ray diffraction can be considered as the reflection of the X-rays off Miller planes in the sample. The spacing of these planes gives the position of the peaks (Bragg's law $n\lambda=2d\sin\theta$) whereas the intensity is given by the position of the repeating units relative to these planes. Miller indices are described by how the plane cuts through the **a**, **b** and **c** unit cell vectors. In the case of MCM-41 **c** is always equal to zero because there is no ordering in the **c** direction.



The dots represent lattice points; the lines are the Miller planes.

6.2 How to Calculate the Loading of an Organic Group on MCM-41 or Silica.

1. The loading of the aminopropyl functionalised MCM-41 is first calculated by the following equation. Loading based on nitrogen elemental analysis (%N). Exactly the same for carbon elemental analysis and silica based compounds.

$$\text{Grams of nitrogen in 1 gram in compound} = \frac{\%\,\text{N} \times 1}{100} = \text{N g}$$

$$\text{mmoles of nitrogen in 1 gram of compound} = \frac{\text{N g} \times 1000}{\text{Atomic mass of Nitrogen}} = \text{N mmol}$$

$$\text{Loading of organic group in mmol g}^{-1} = \frac{\text{N mmol}}{\text{no. of atoms of nitrogen in organic group}}$$

2. Theoretical elemental analysis for subsequent MCM-41 base compounds is then calculated based on the maximum loading. For the new compound, that is the loading of the aminopropyl functionalised MCM-41 calculated above. The example is given for nitrogen but exactly the same applies for carbon and hydrogen.

$$\text{mmoles of nitrogen in 1 gram of compound} = \text{Loading} \times \text{no. of atoms of N in organic group} = \text{N mmol}$$

$$\text{Grams of nitrogen in 1 gram in compound} = \text{N mmol} \times \text{atomic mass of N} = \text{N g}$$

$$\text{Theoretical percentage of N} = \frac{\text{N g} \times 100}{1} = \%\,\text{N}$$

3. $$\text{Yields of reactions} = \frac{\text{observed \% of nitrogen} \times 100}{\text{theoretical \% of nitrogen}}$$

6.3 Surface area calculations for MCM-41

The following are approximate calculations to give some indication of the percentage of the surface that is external. Diagrams are not to scale.

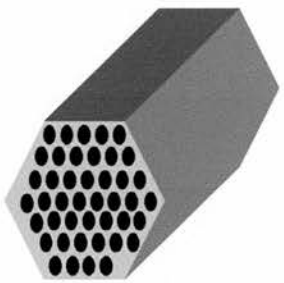


Fig 1 - Whole particle

Fig 2 - Pore plus associated wall.

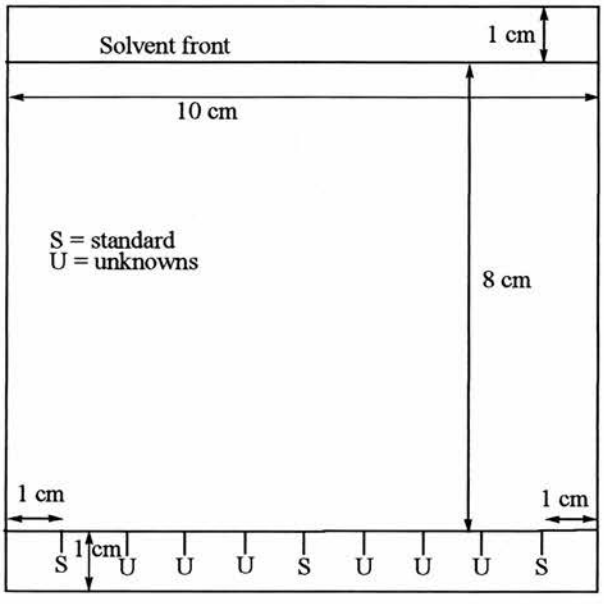
Assumptions:

- particle size is 16 μm x 16 μm x 16 μm
- pore diameter 30 Å
- wall diameter between pores is 5 $Å^2$

If the particles are the minimum size that will not pass through a grade 3 sinter funnel, then the percentage of surface area which is external is 0.03 %.

All numbers are in micrometres		
Particle size	16	16
Length of hexagonal walls of particle Fig 1	9.24	
Surface Area of particle if no pores	1330.22	
Pore radius	1.50E-03	
wall thickness between pores	5.00E-04	
Pore diameter	3.50E-03	
Length of hexagonal walls Fig 2	2.02E-03	
Pore cross sectional area	7.07E-06	
Cross-sectional area of hexagonal in Fig 2	1.06E-05	
Number of pores	20897959.18	
Total external surface area	1034.78	
Total internal surface area	3151633.44	
% surface which is external	**0.03**	

6.4 Determination of Rates of Reactions for PLL Catalysed Epoxidations Using TLC.



Standards for both the starting material and product were spotted and the unknown concentrations were spotted in duplicate and averaged.

6.5 Preparation of TLC Dips.

1. 5 % PMA Dip.

To prepare the dip phosphomolybdic acid (12.5 g) was dissolved in ethanol (250 ml). A plate is dipped in this solution were then heated with a heat gun to give dark green spots on a pale green background. This is a useful general dip to stain many different types of structures.

2. 0.33 % Ninhydrin Dip.

To prepare this dip Ninhydrin (0.825 g) was dissolved in acetone (250 ml). A plate dipped in solution then heated gently with a heat gun to give purple or orange spots on a pale pink background. This dip is for mainly primary amines, which give the purple stop. Secondary amines give a paler orange spot.

3. Ce /Mo Dip.

In water (942 ml) cerium sulphate dihydrate (10 g) and ammonium molybdate tetrahydrate (15 g) were added and then conc. H_2SO_4 (58 ml) was added slowly. A plate dipped in solution then heated with a heat gun to give white spots on a dark blue background. This is another general dip as for PMA.

4. Kaiser test.[3]

Solution 1 – Ninhydrin (1 g) was dissolved in ethanol (20 ml).

Solution 2 – Potassium cyanide (1 mM solution, 12 ml) was dissolved in pyridine (40 ml)

Solution 3 – Phenol (80 g) was dissolved in ethanol (20 ml)

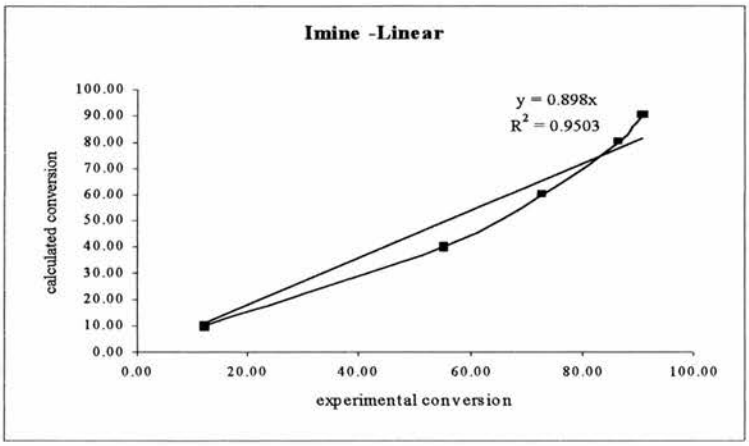
Two drops of each solution were added to the substrate which can either be in solution or a solid. The mixture was heated to 60 °C for 5 min. If a primary amine is

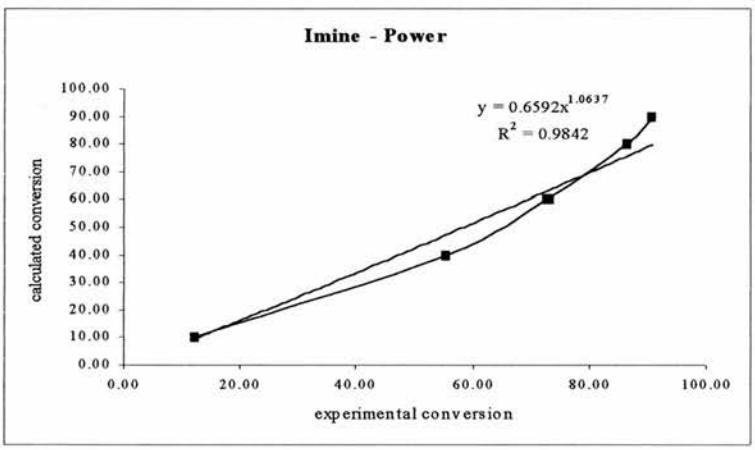
present then the colour changes from yellow to dark blue. This test is a more sensitive ninhydrin test, which is particularly useful for checking free primary amines on a solid phase.

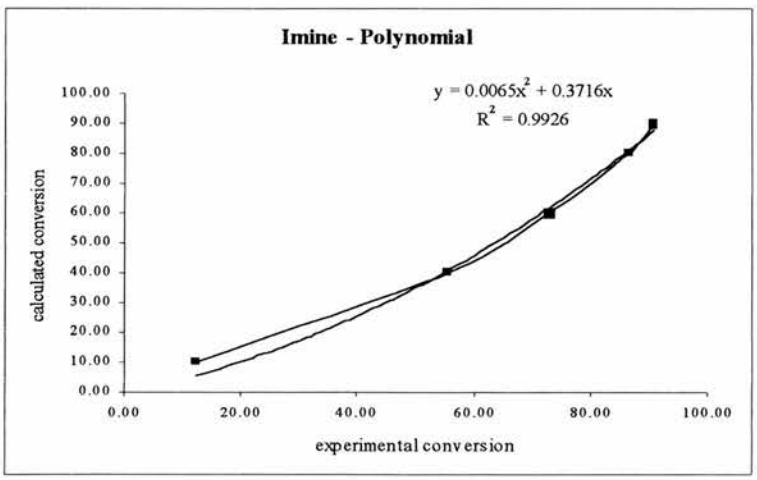
6.6 Calibration Graphs for Calculating Conversion from HPLC in the Imine and Ketone Reductions. (Chapter 5)

6.6.1 Imine (52)/ Amine (54)

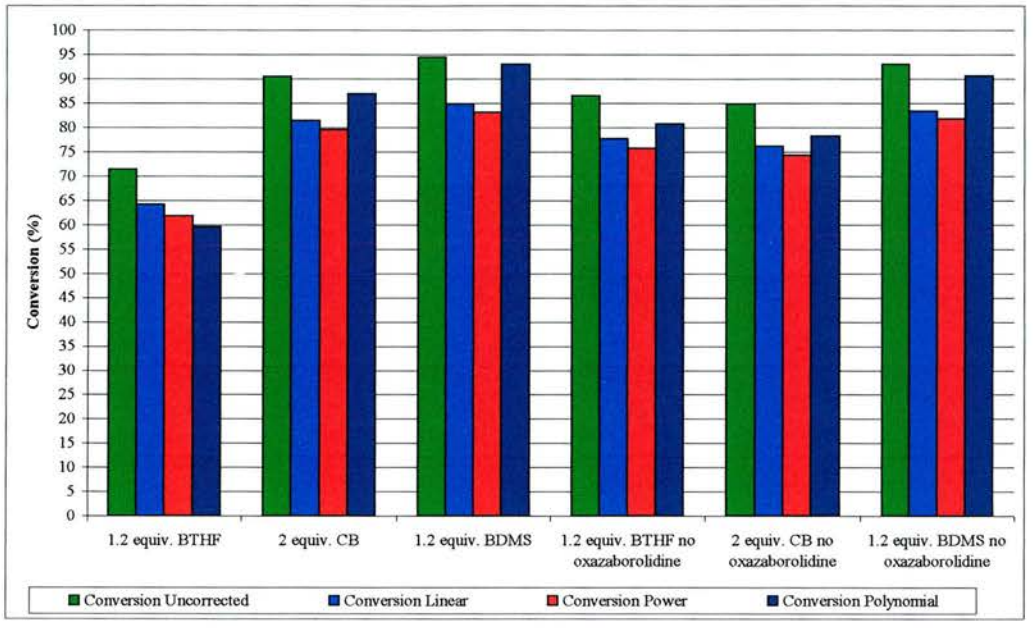
Calibration graphs with different best fit lines.







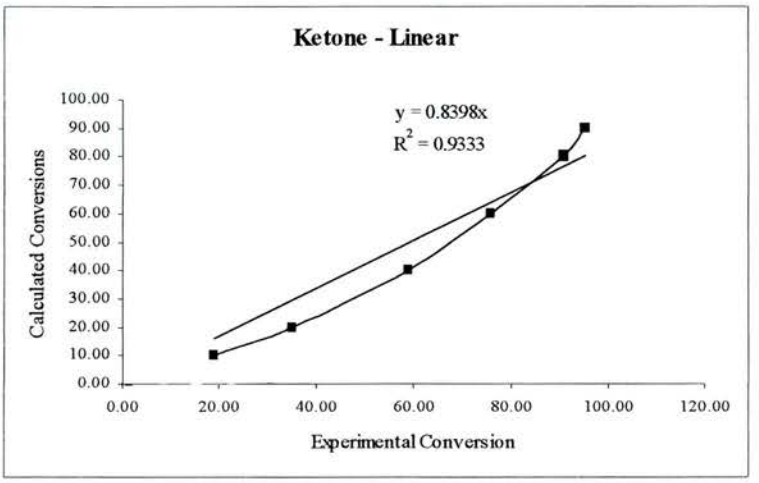
Difference between the conversions calculated from the different best fit lines.

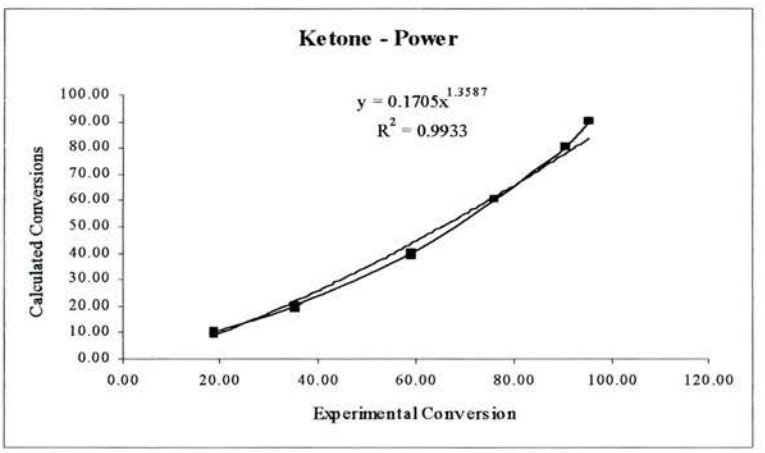


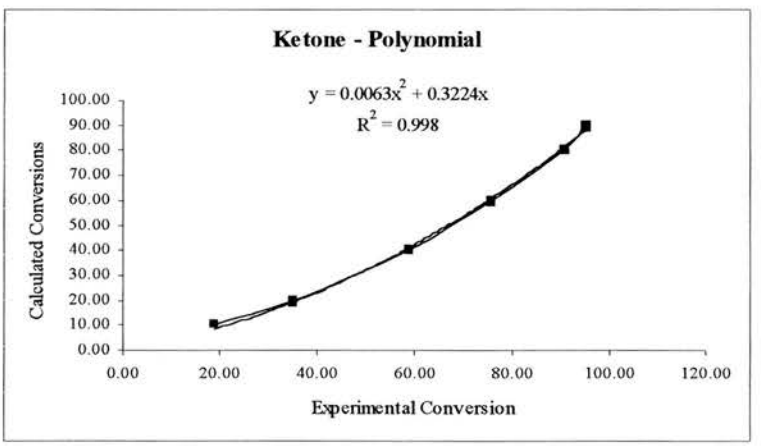
Therefore, uncorrected conversions used in Results and Discussion in Chapter 5.

6.6.2 Acetophenone/ Alcohol ***(55)***

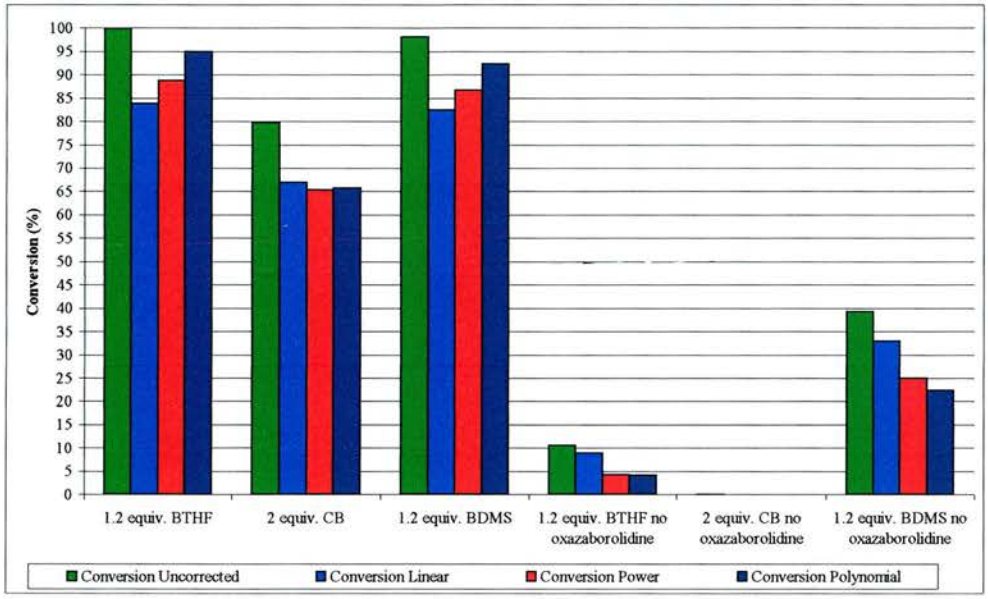
Calibration graphs with different best fit lines.







Difference between the conversions calculated from the different best-fit lines.



Therefore, uncorrected conversions used in Results and Discussion in Chapter 5.

6.7 Raw Data from the HPLC on the Investigation of Borane Reduction of Imine (52) and Acetophenone. (Chapter 5).

The results from each set of condition are shown by two graphs. The first graph shows the uncorrected data and the second graph shows the corrected data. This means the first graphs show the observed e.e. and conversions. The second graph shows the observed e.e. minus the e.e. from the reaction with no oxazaborolidine present, likewise for the conversion. This applies to all conditions except where no oxazaborolidine was present and the effect of temperature where only the observed e.e. and conversions are quoted.

Therefore:

- Positive e.e. = R enantiomer of amine **(54)** or alcohol **(55)**
- Negative e.e. = S enantiomer of amine **(54)** or alcohol **(55)**

In corrected graph:

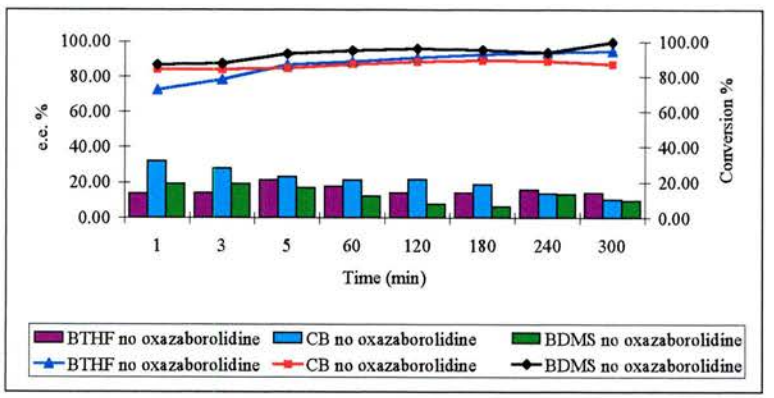
- Positive conversion = Observed conversion is larger than conversion form uncatalysed reaction.
- Conversion is 0 = Observed conversion is same as the conversion form uncatalysed reaction.
- Negative conversion = Observed conversion is less than conversion form uncatalysed reaction.
- If the conversion decreases then it means that it started off at one value and over time it has not changed however, over time the conversion form the uncatalysd reaction increases. Therefore the corrected conversion decreases.

On all the graphs the bars are the e.e. and the lines the conversion.

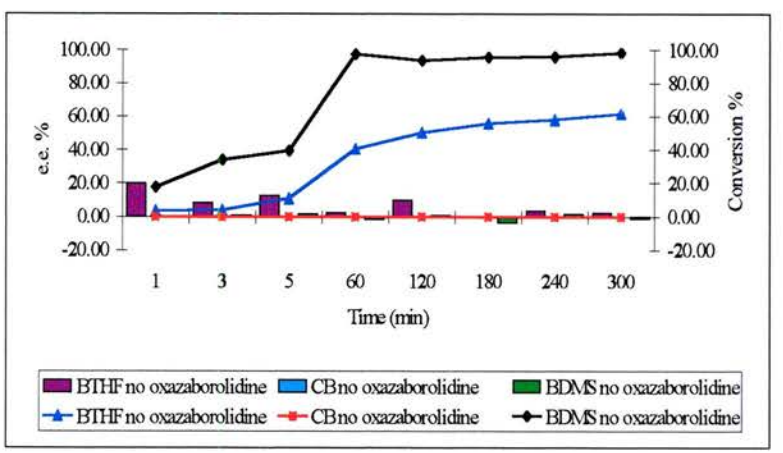
Solution Phase Reductions.

Effect of no oxazaborolidine.

Imine:

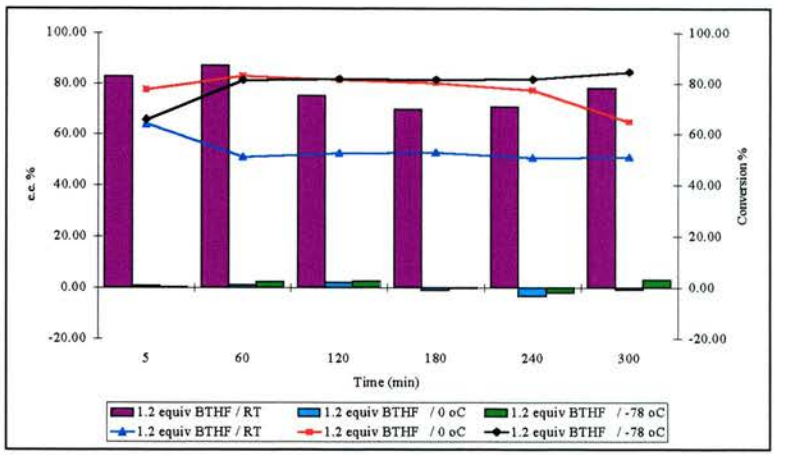


Ketone:

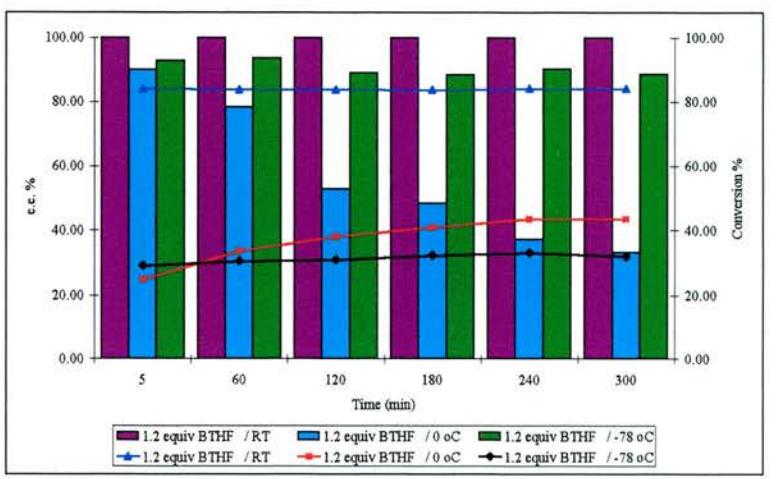


Effect of Temperature.

Imine:

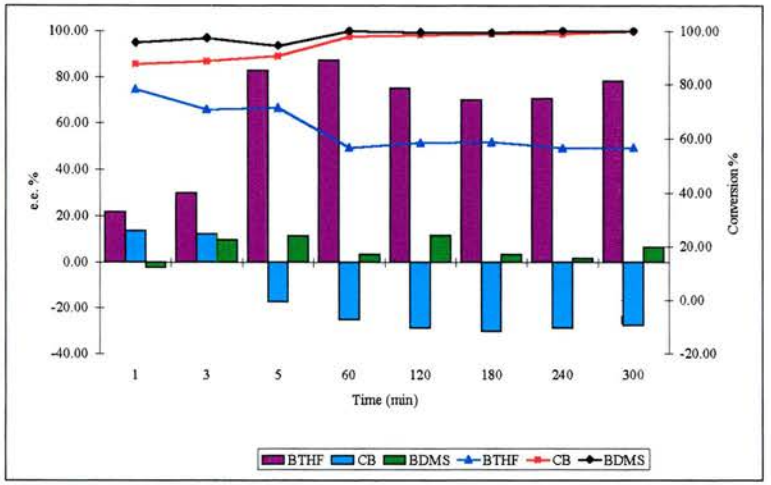


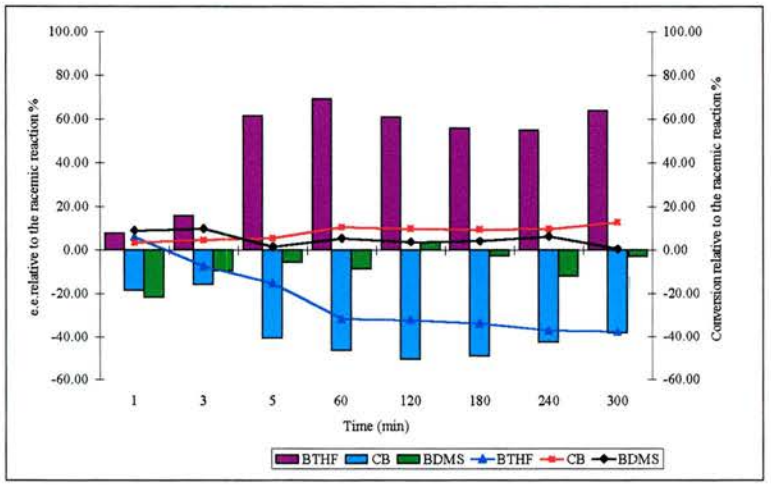
Ketone:



Effect of Reducing agent.

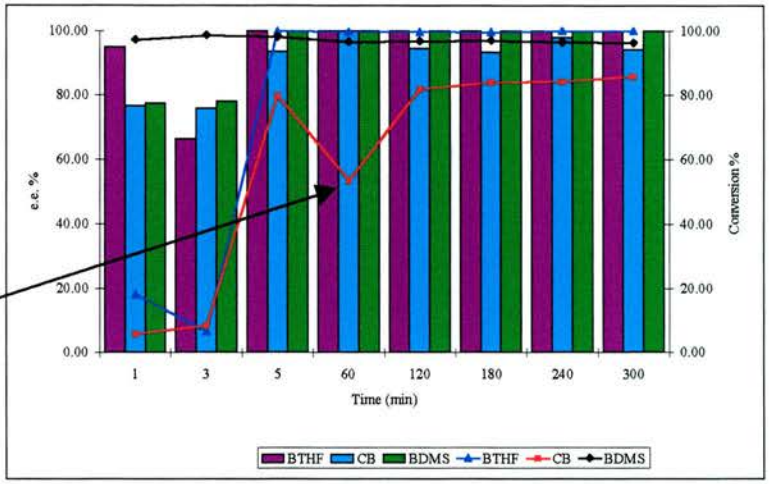
Imine:

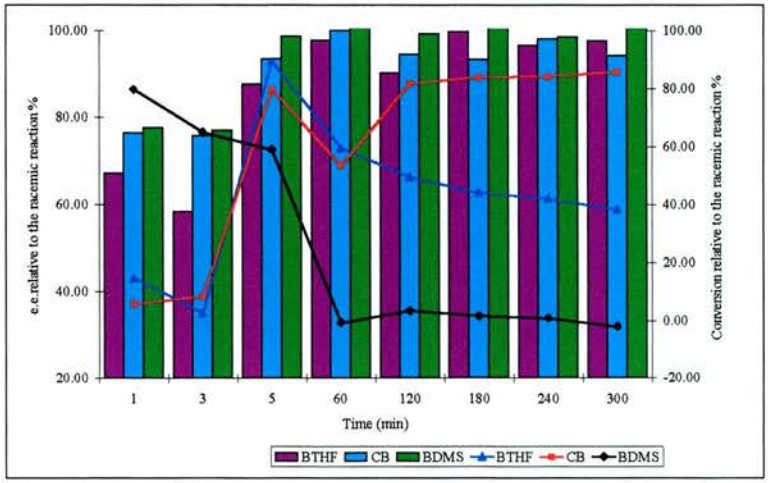




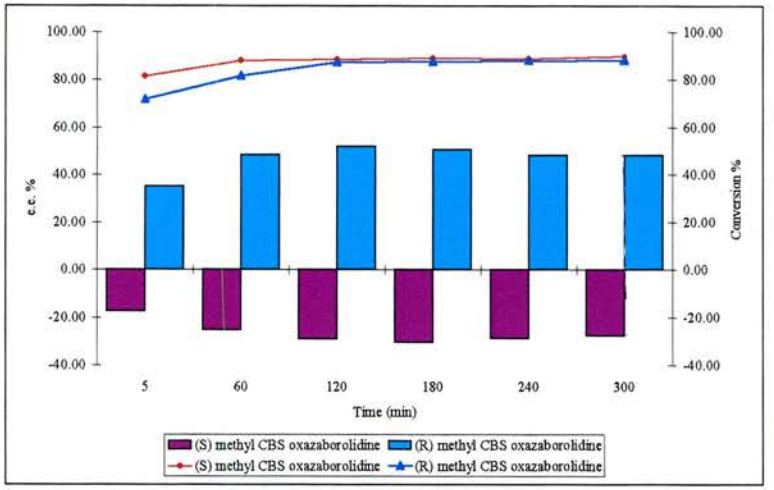
Ketone:

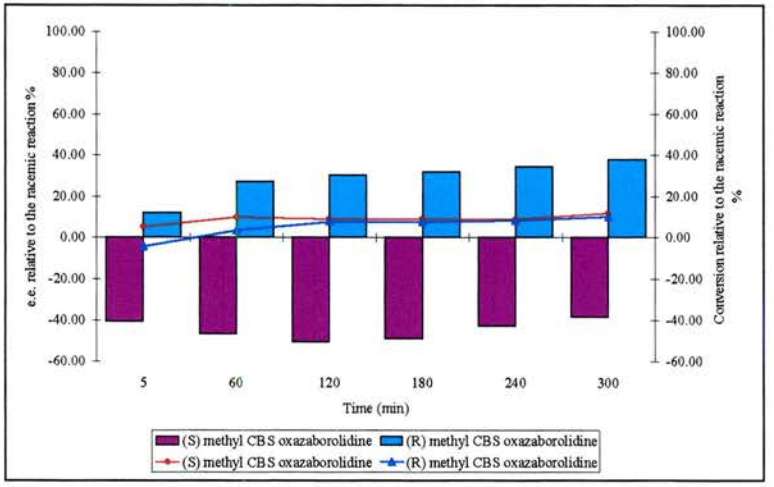
Error





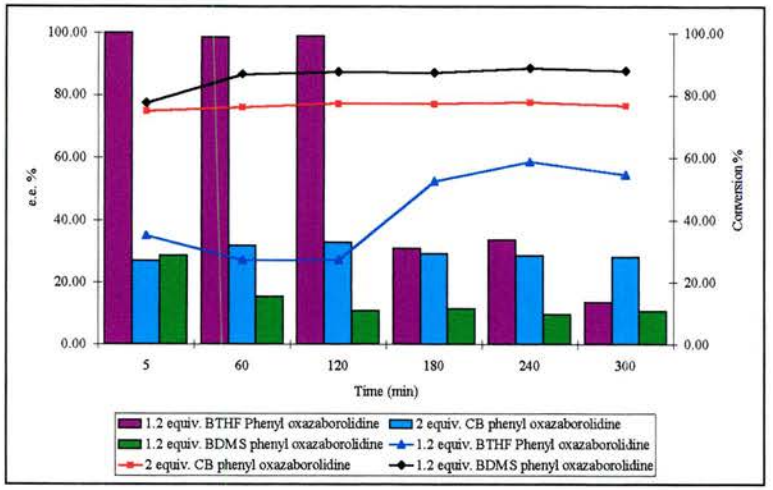
Effect of Catecholborane on Imine reduction.

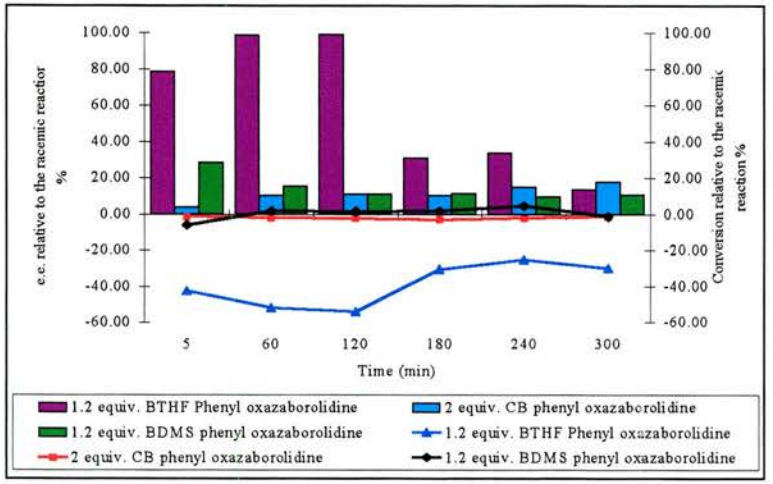




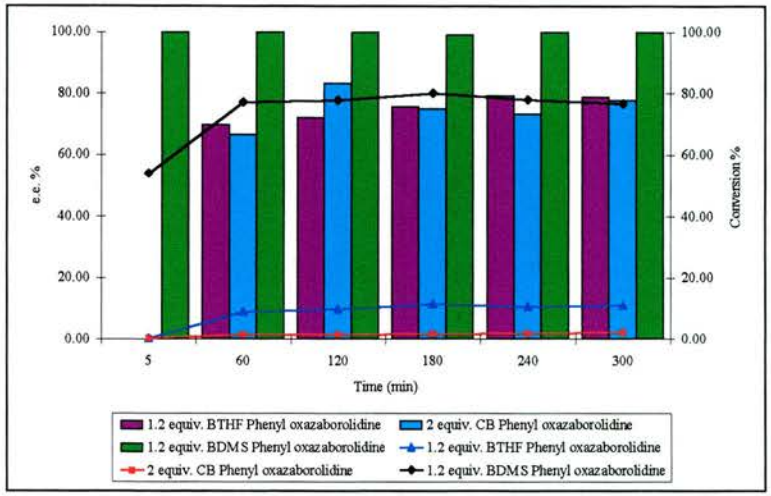
Effect of Phenyl oxazaborolidine.

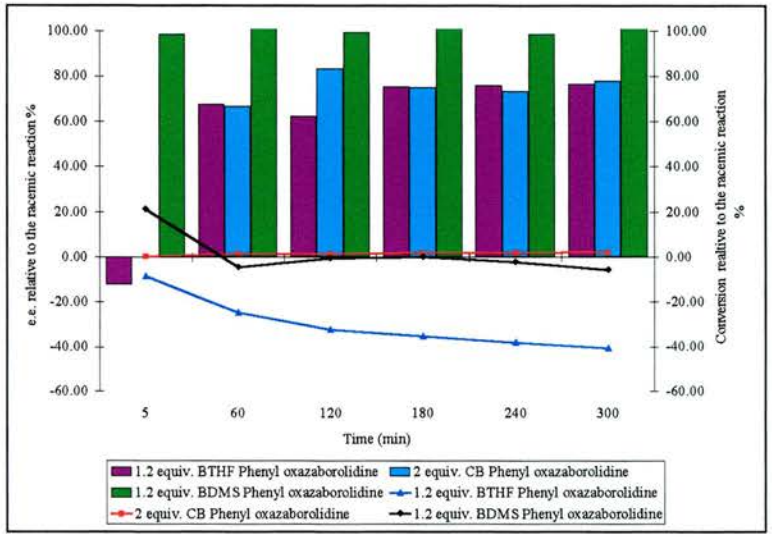
Imine:





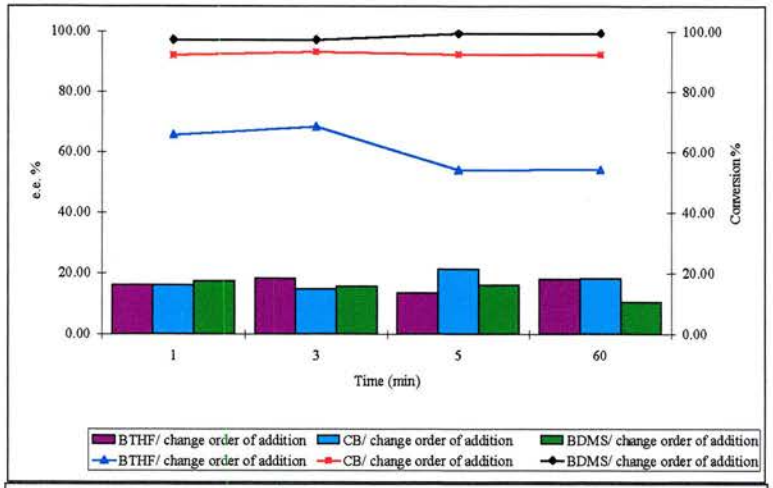
Ketone:

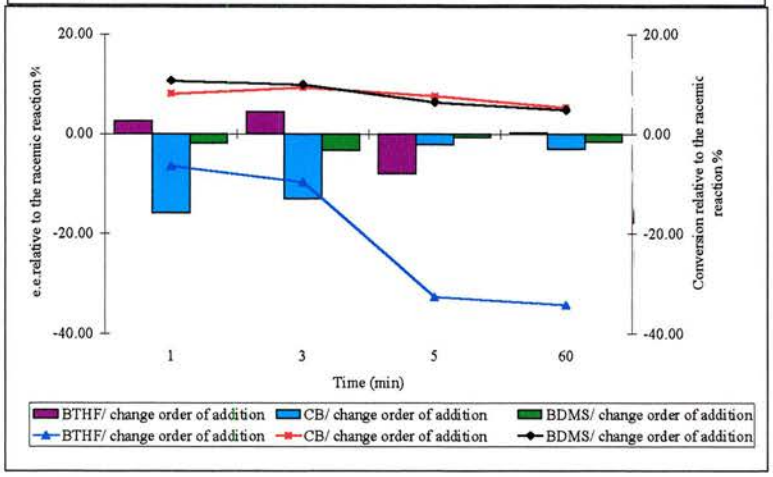




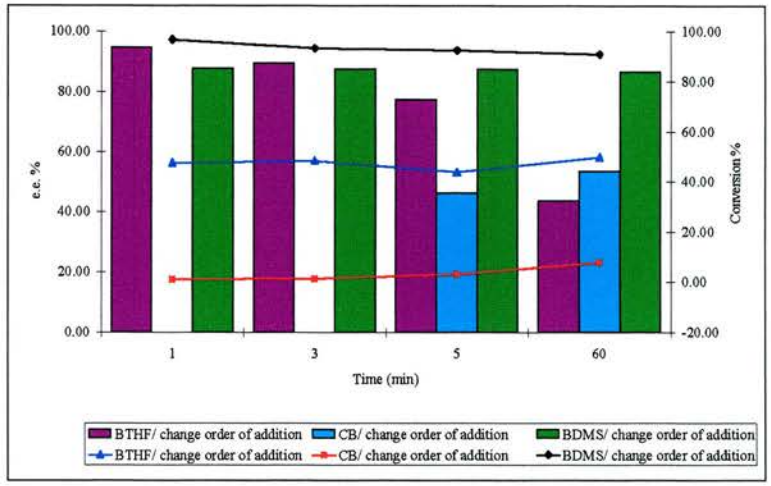
Effect of changing the order of addition on the solution phase reduction. (Borane + oxazaborolidine, then add substrate)

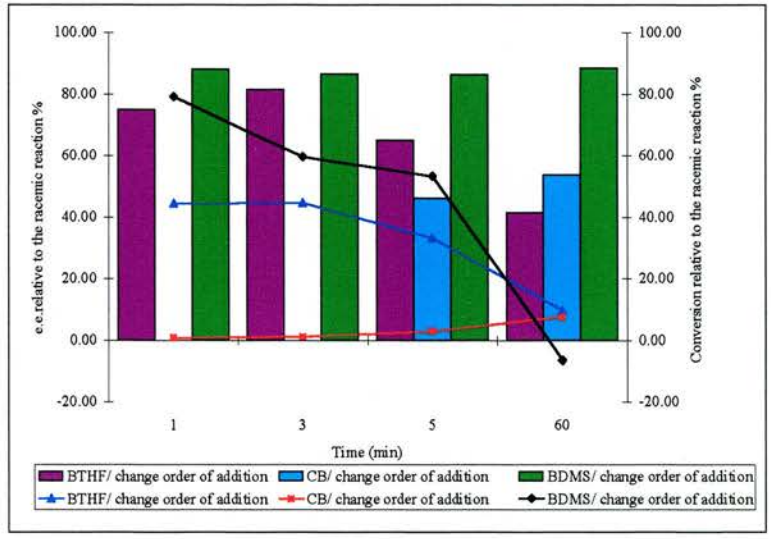
Imine:





Ketone:

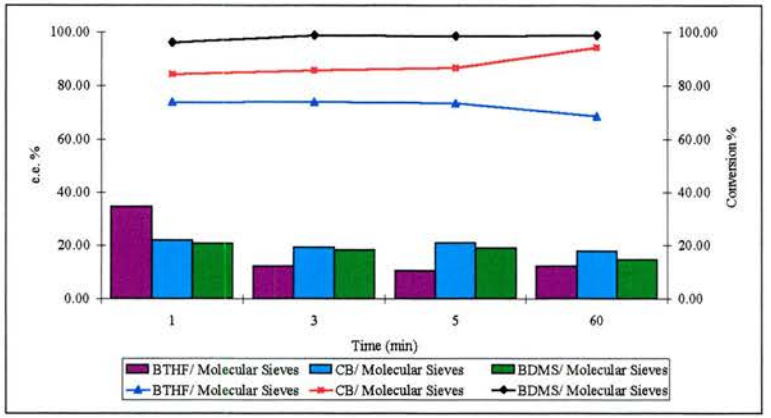


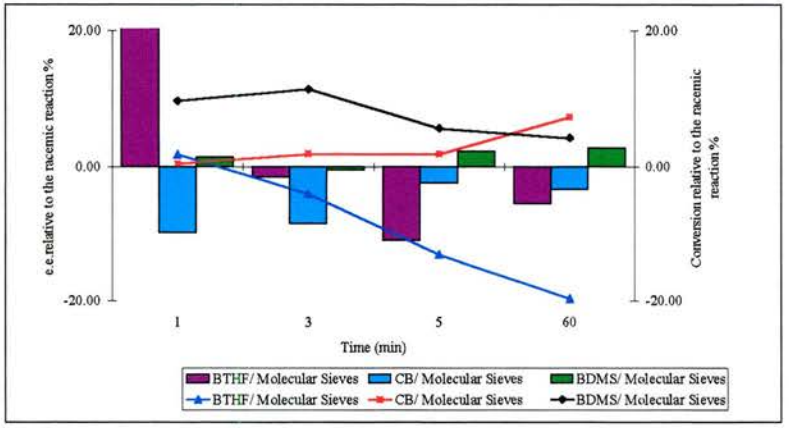


Effect of silicates on Solution Phase Reductions.

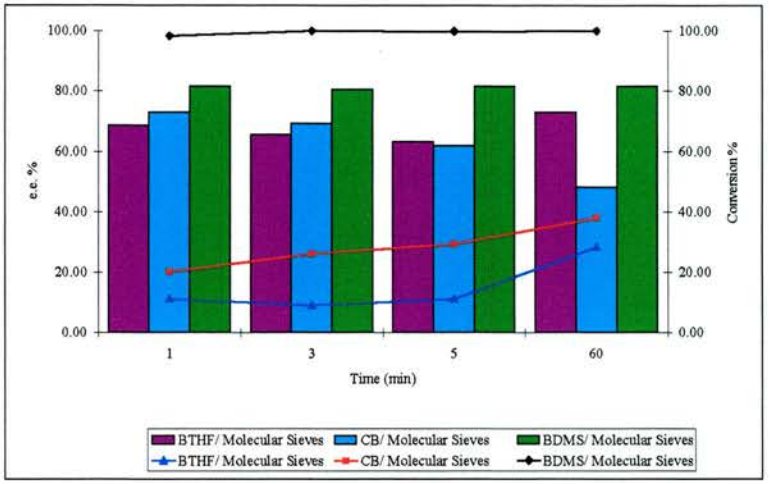
Effect of molecular sieves on solution phase asymmetric reduction.

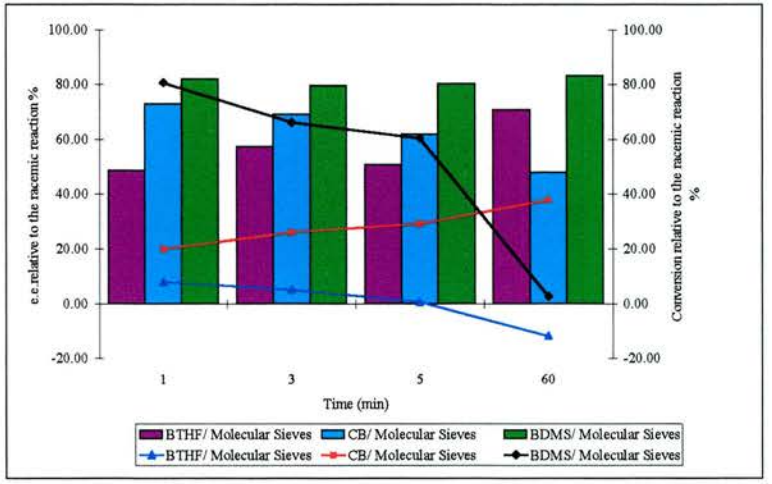
Imine:





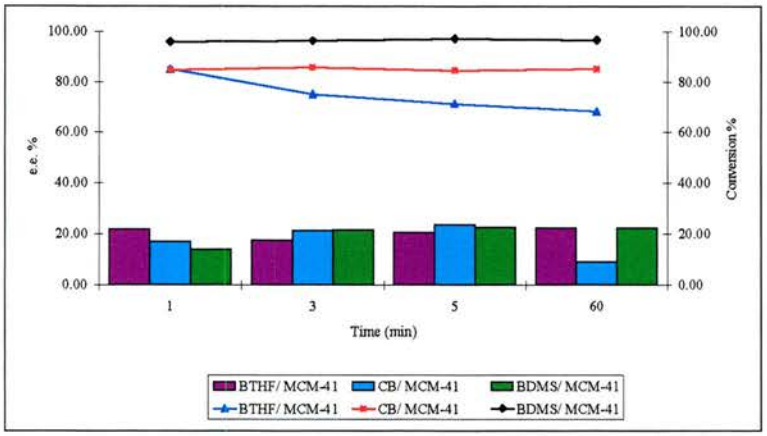
Ketone:

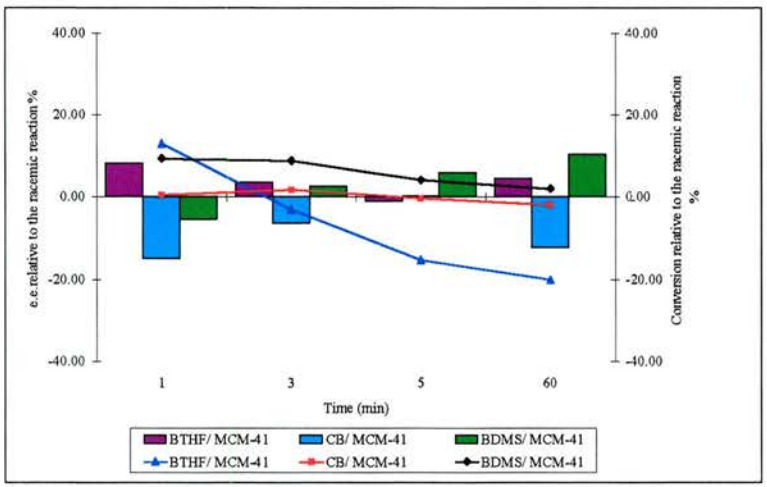




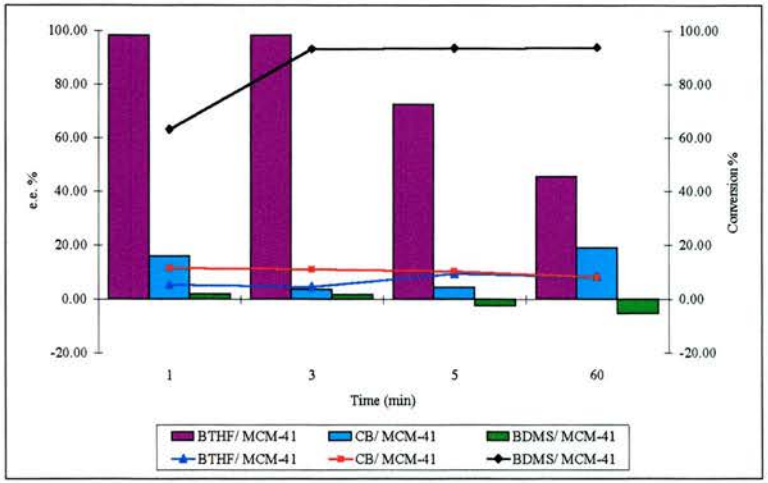
Effect of a MCM-41 slurry on the solution phase asymmetric reduction.

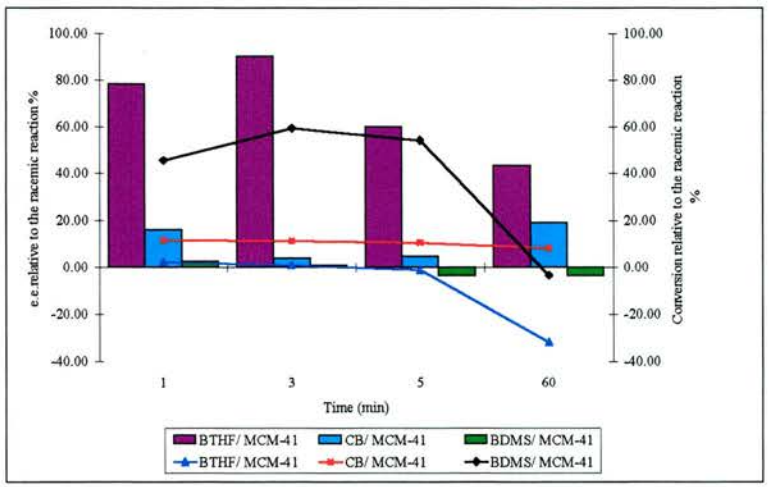
Imine:





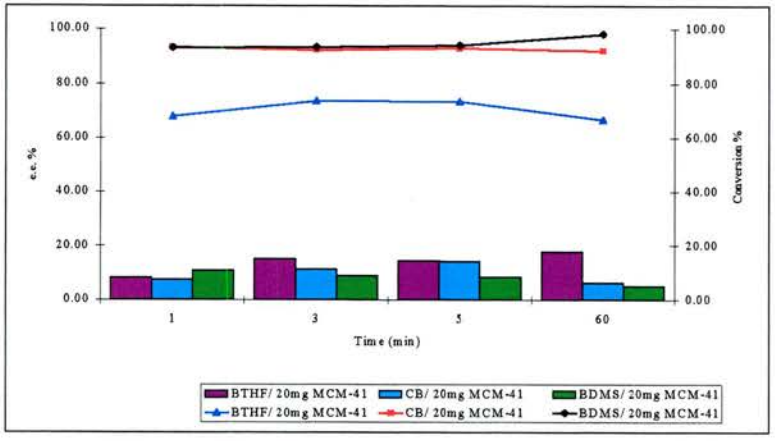
Ketone:

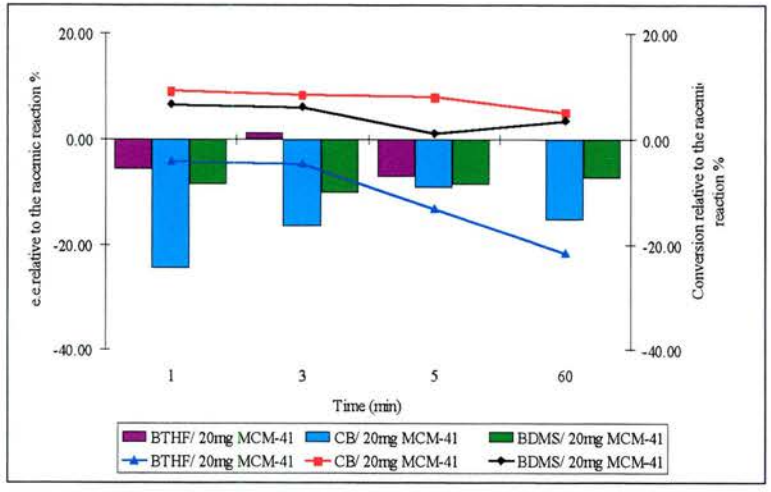




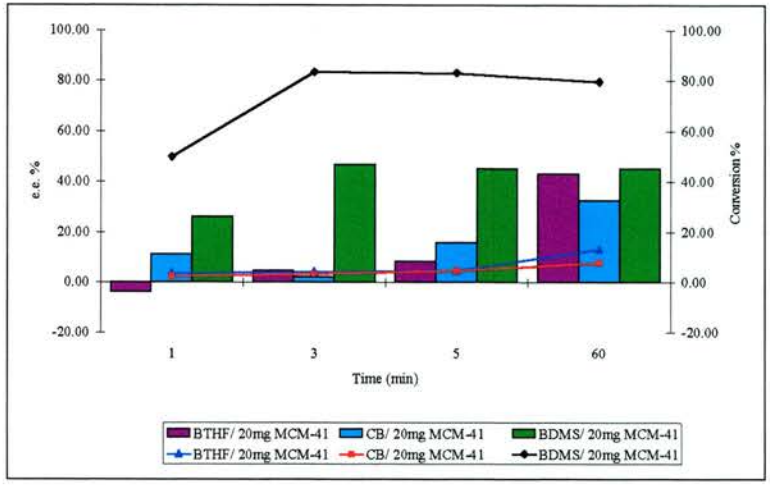
Effect of 20 mg of MCM-41 on the solution phase asymmetric reductions (1/10th the amount of MCM-41 as in the slurry)

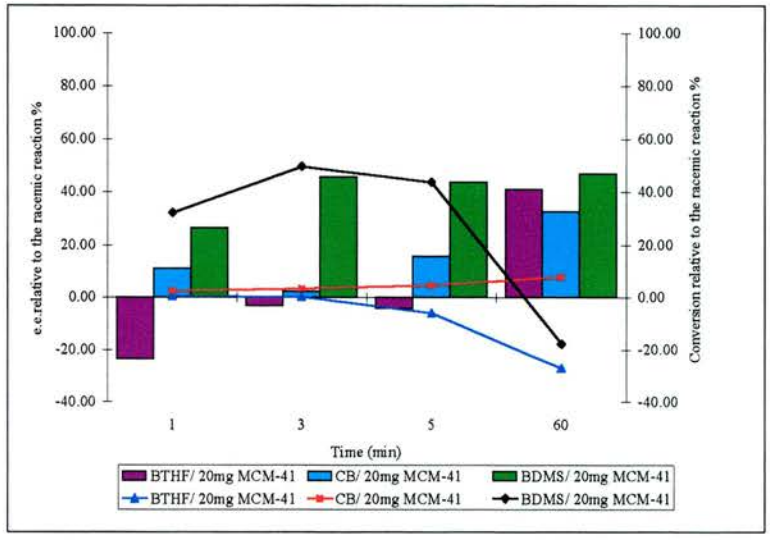
Imine:





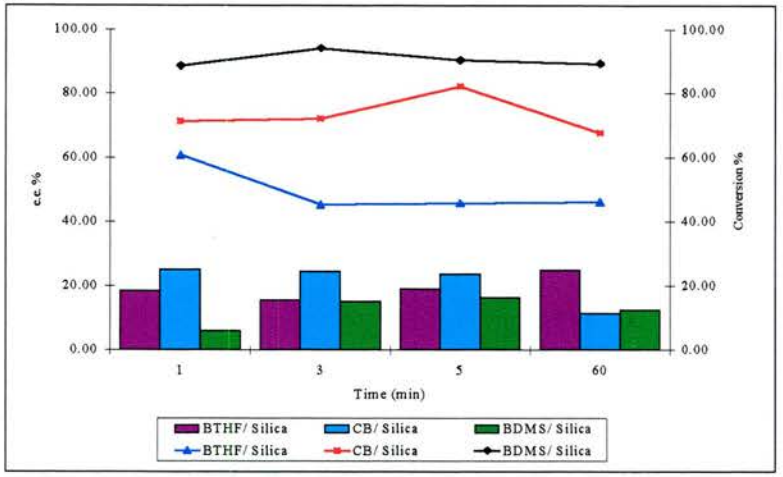
Ketone:

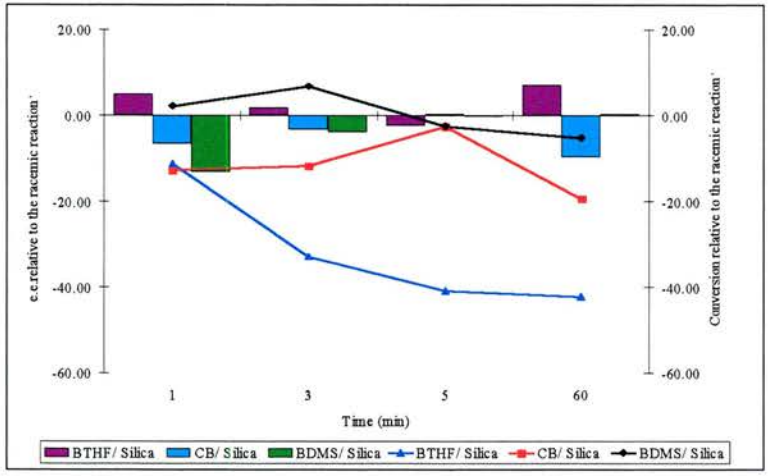




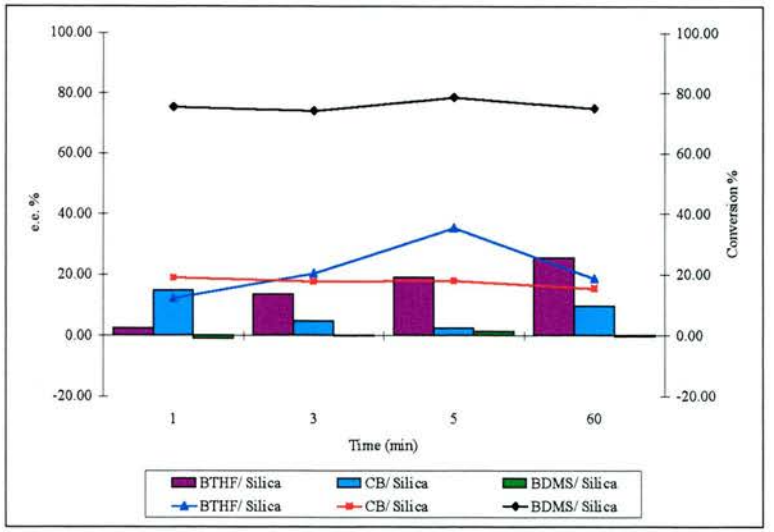
Effect of a silica slurry on the solution phase asymmetric reductions.

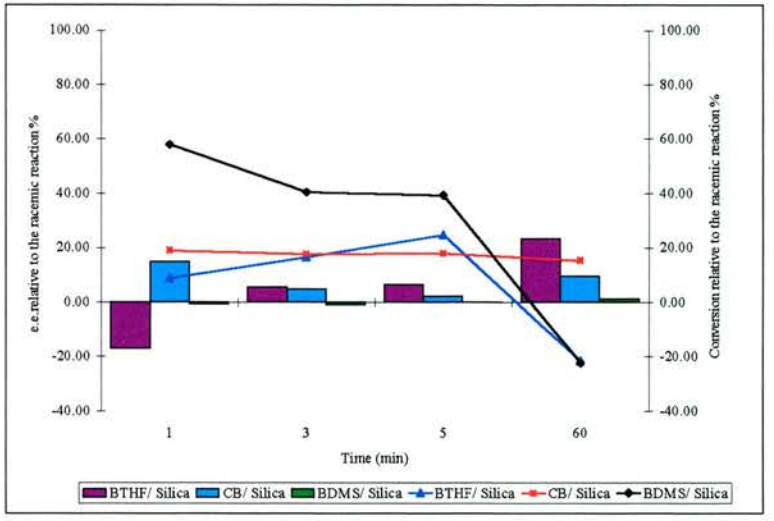
Imine:





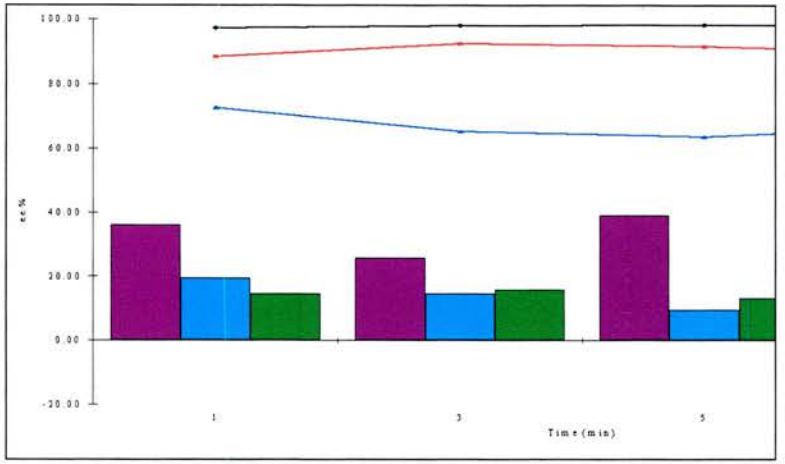
Ketone:

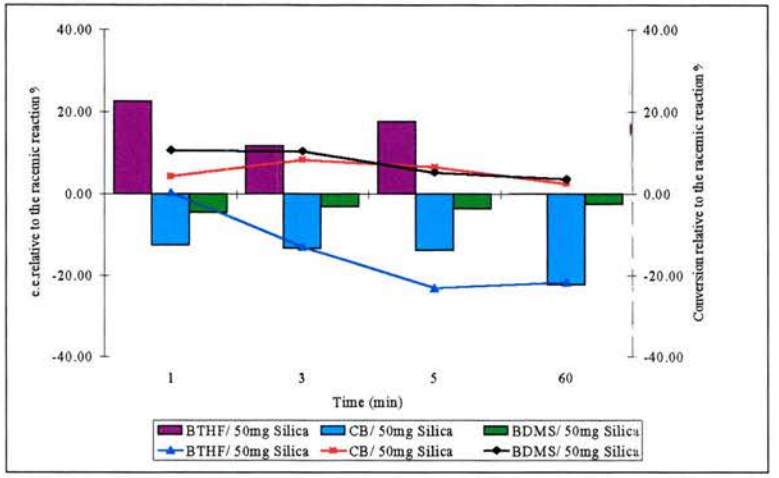




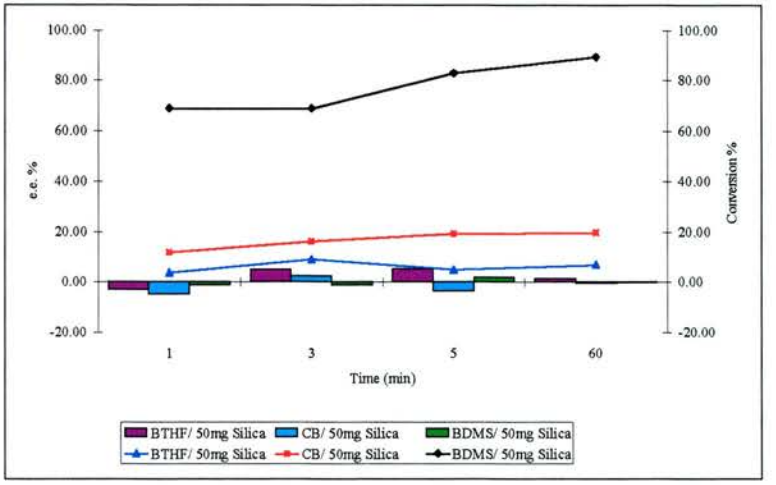
Effect of 50 mg silica on the asymmetric solution phase asymmetric reduction (1/10th the amount of silica as in the slurry).

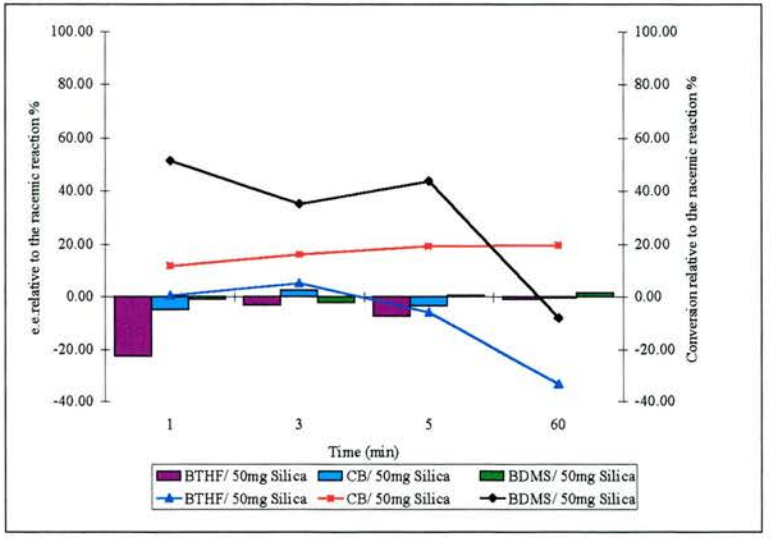
Imine:





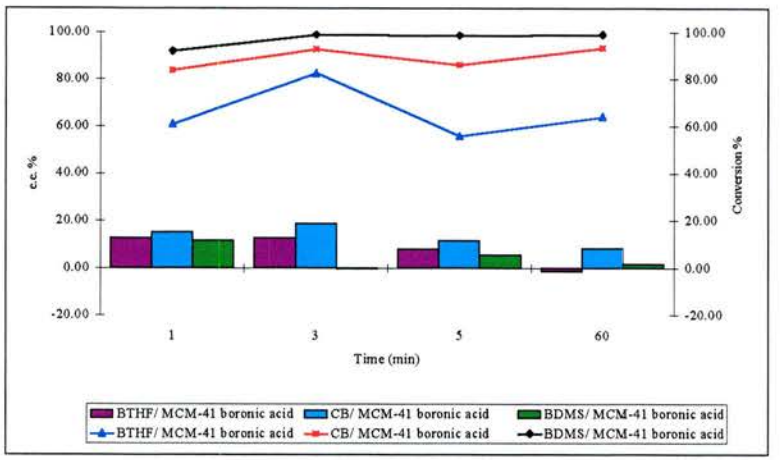
Ketone:

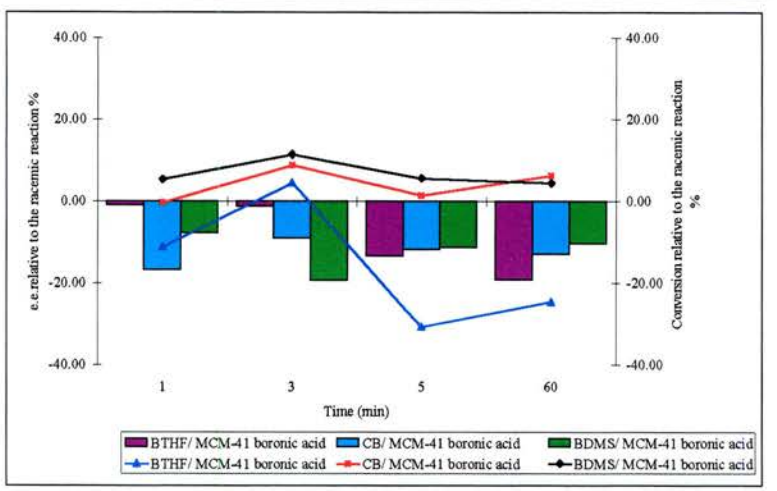




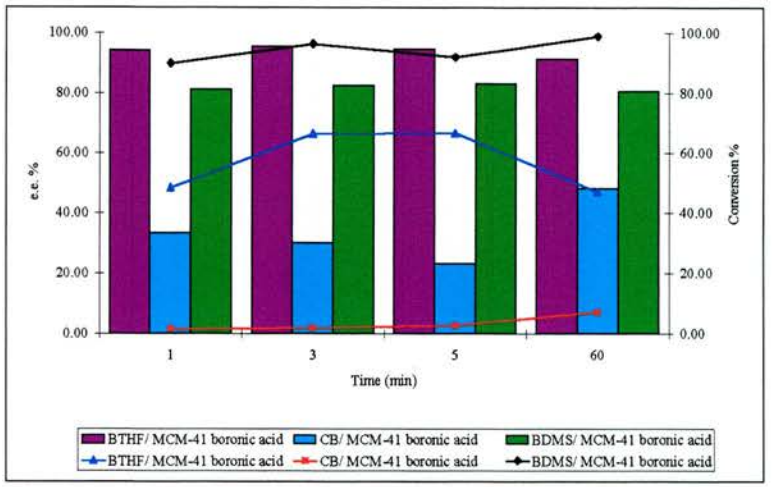
Effect of 0.1 equivalent of MCM-41 supported boronic acid on the solution phase asymmetric reaction.

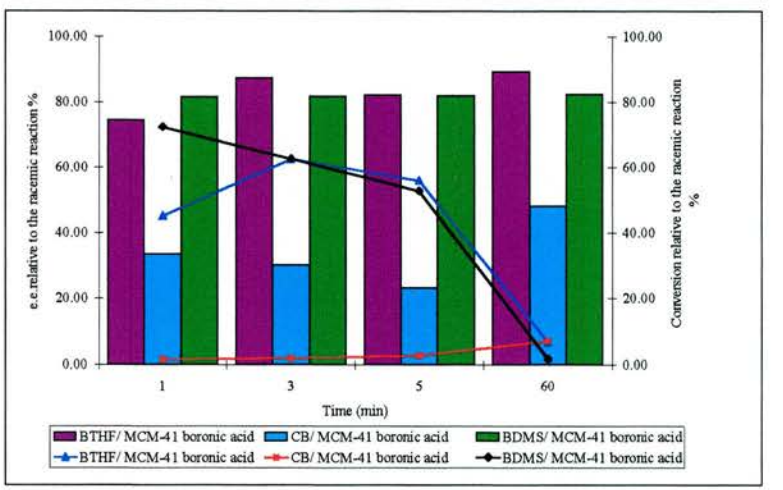
Imine:





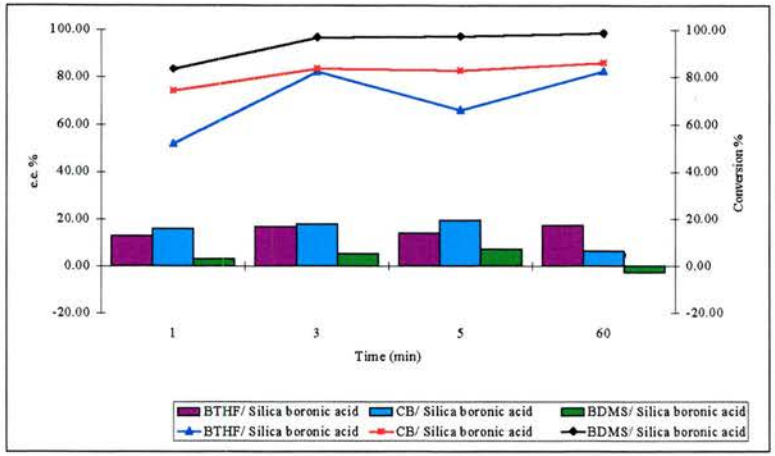
Ketone:

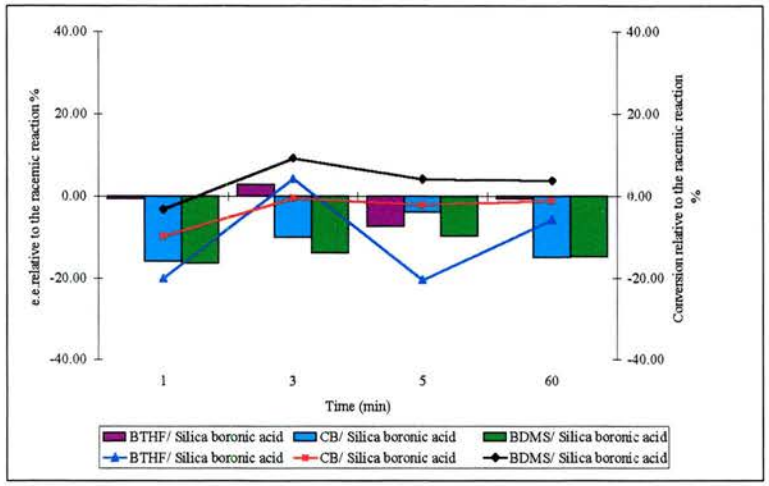




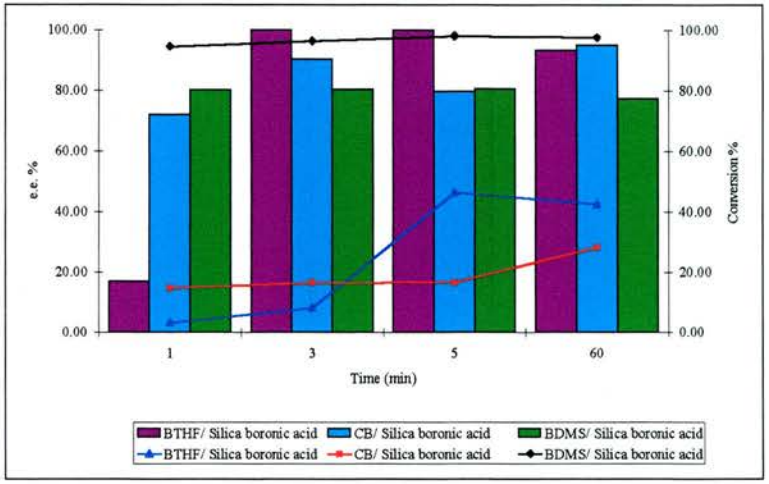
Effect of 0.1 equivalents of silica supported boronic acid on solution phase asymmetric reduction.

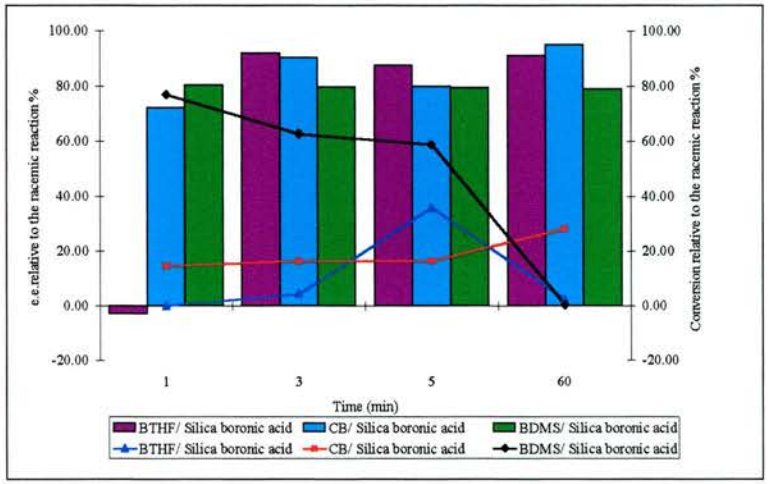
Imine:





Ketone:

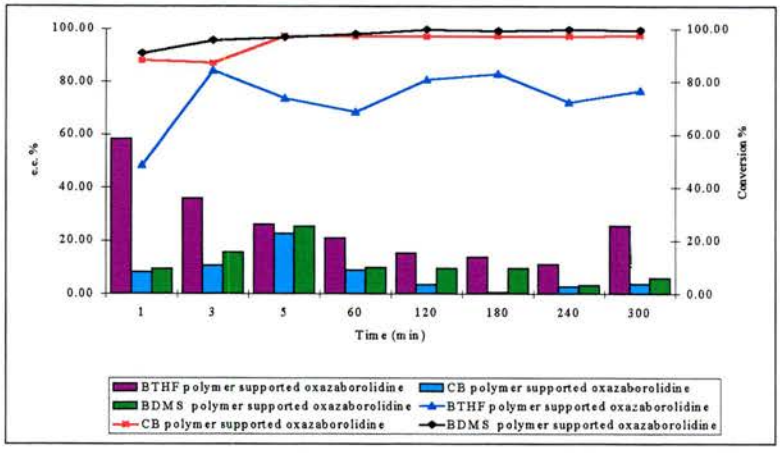


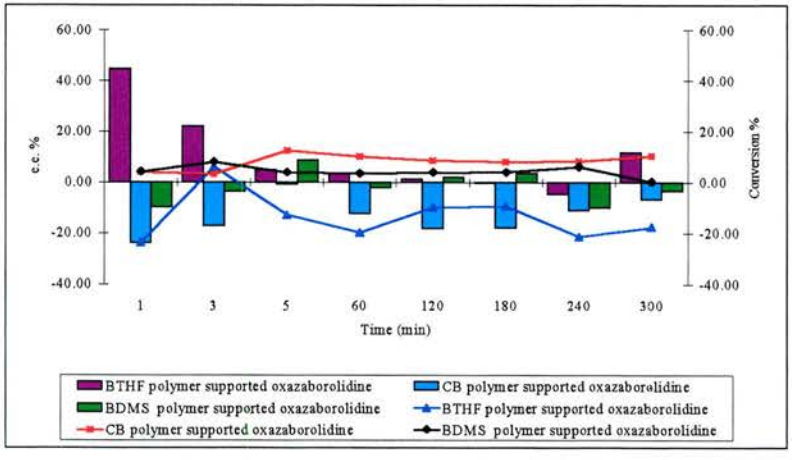


Effect of solid supported oxazaborolidines.

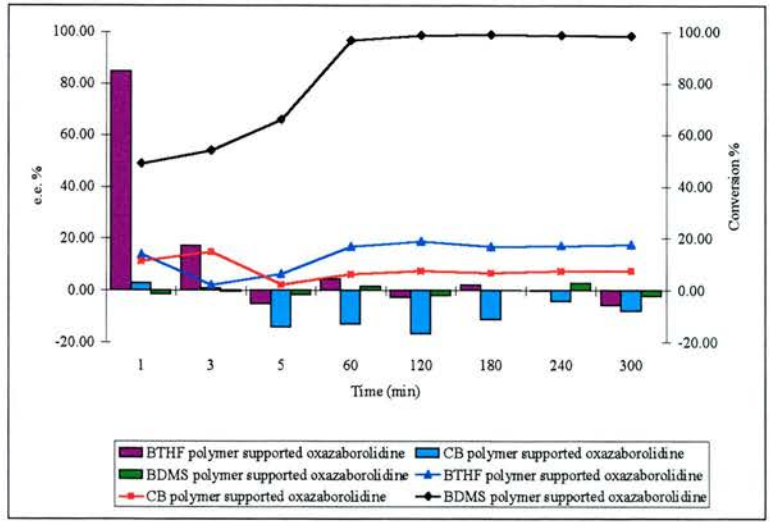
Effect of 0.1 equivalents of polymer bound oxazaborolidine.

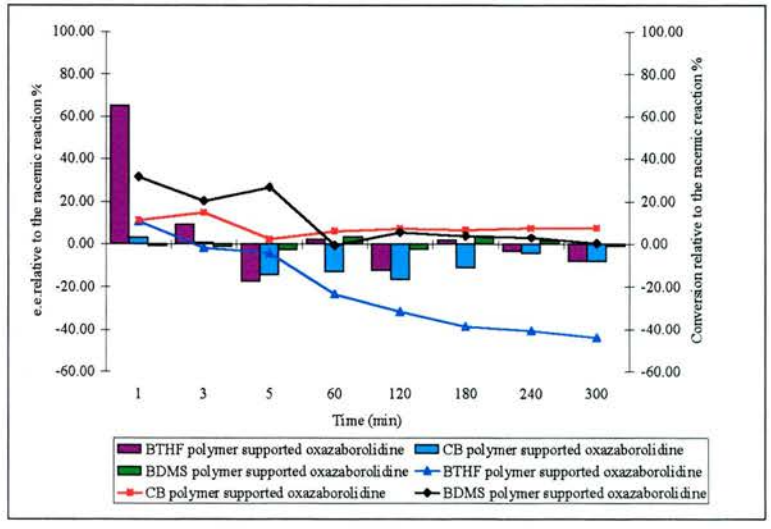
Imine:





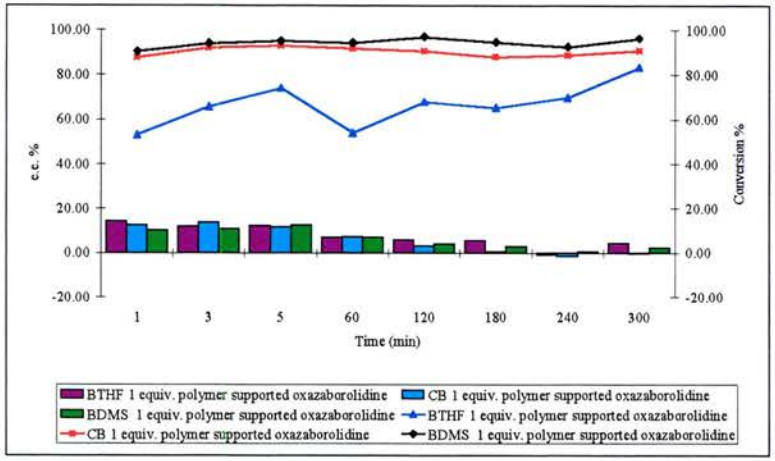
Ketone:

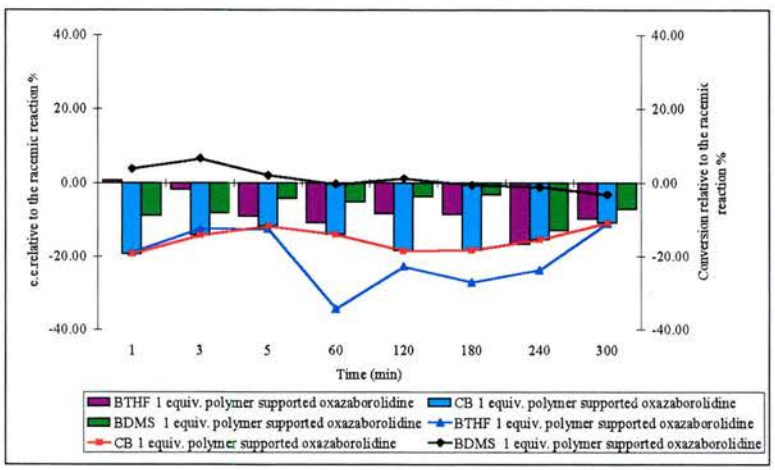




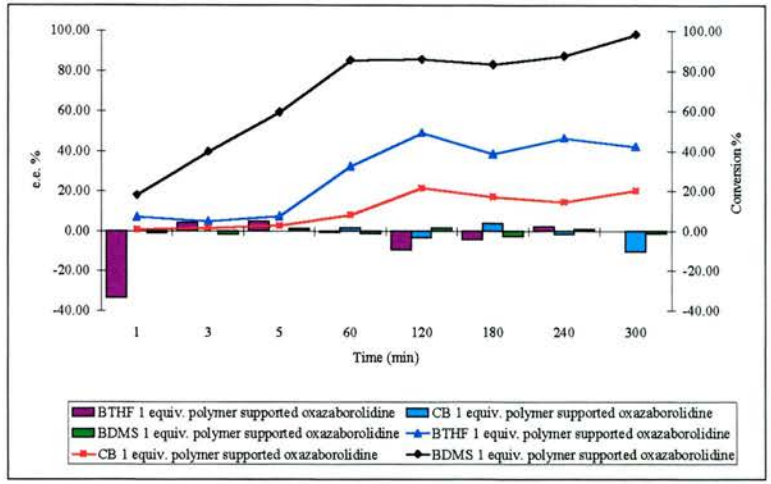
Effect of 1 equivalent polymer bound oxazaborolidine.

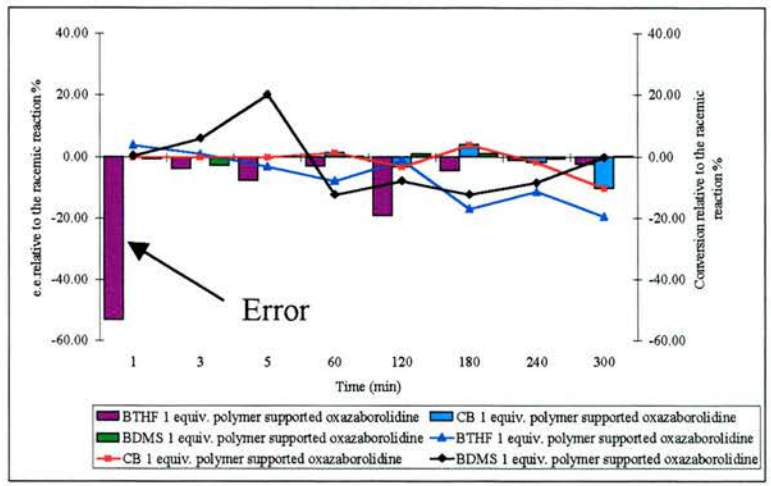
Imine:





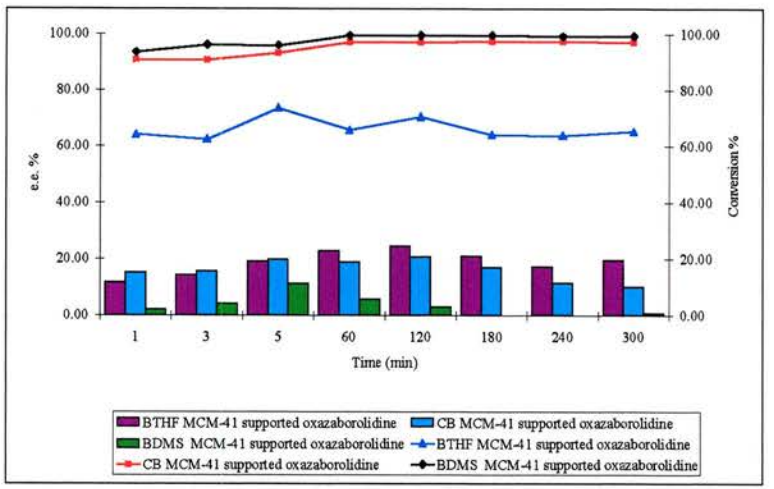
Ketone:

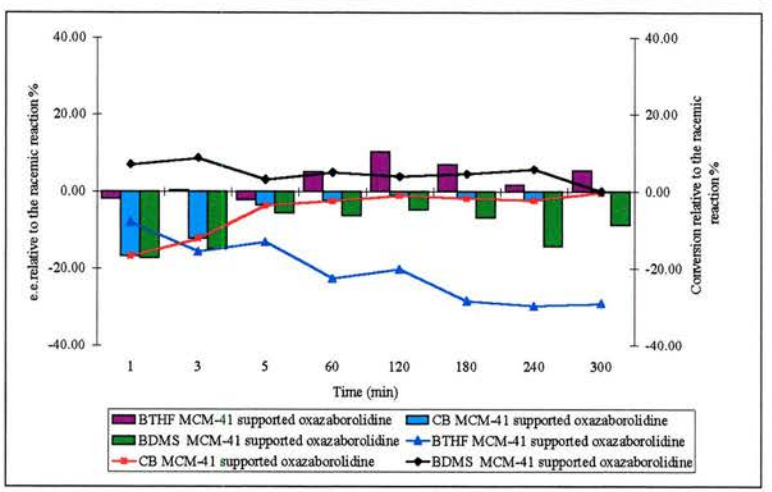




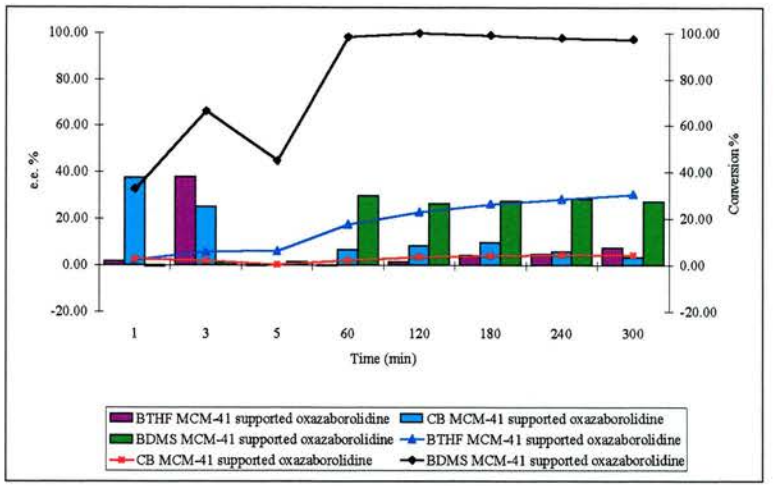
Effect of 0.1 equivalents of MCM-41 supported oxazaborolidines.

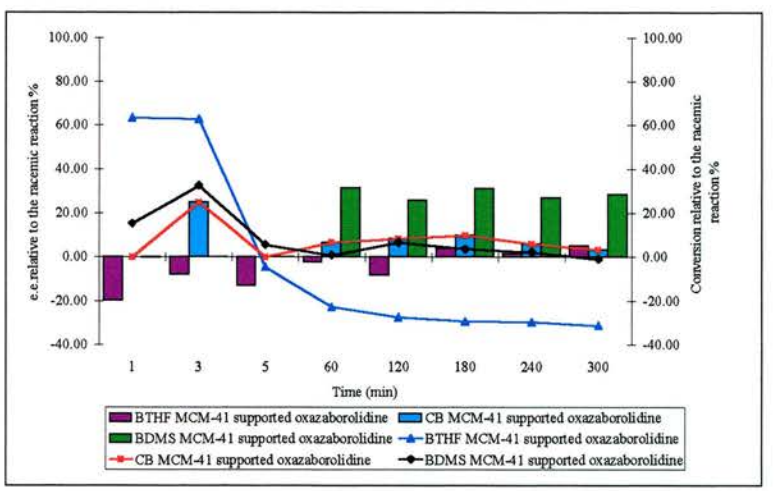
Imine:





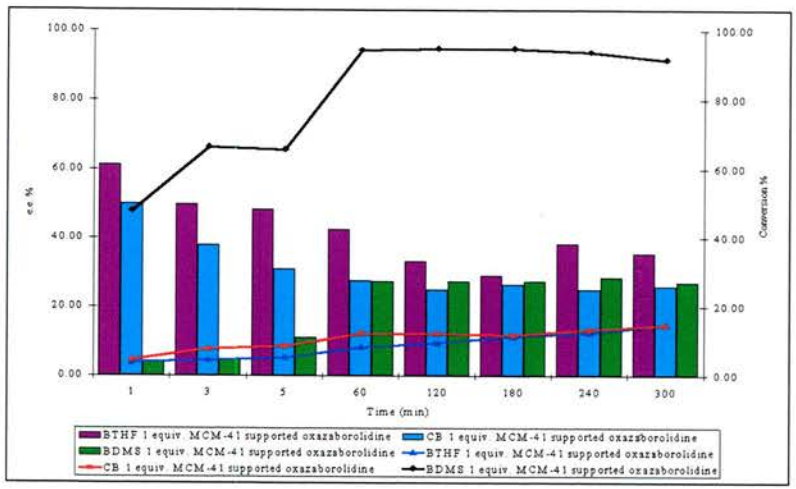
Ketone:

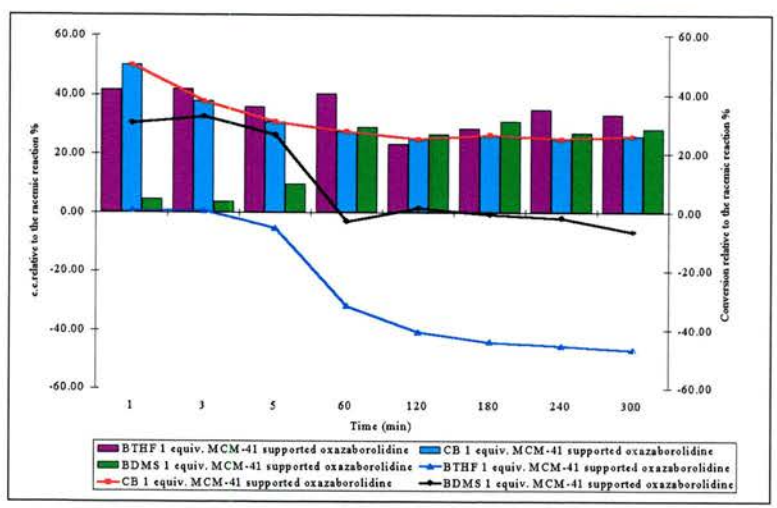




Effect of 1 equivalent MCM-41 supported oxazaborolidine.

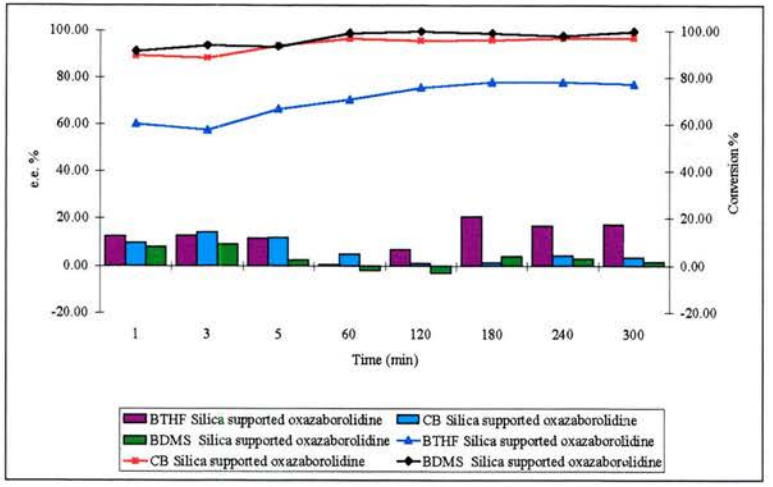
Ketone:

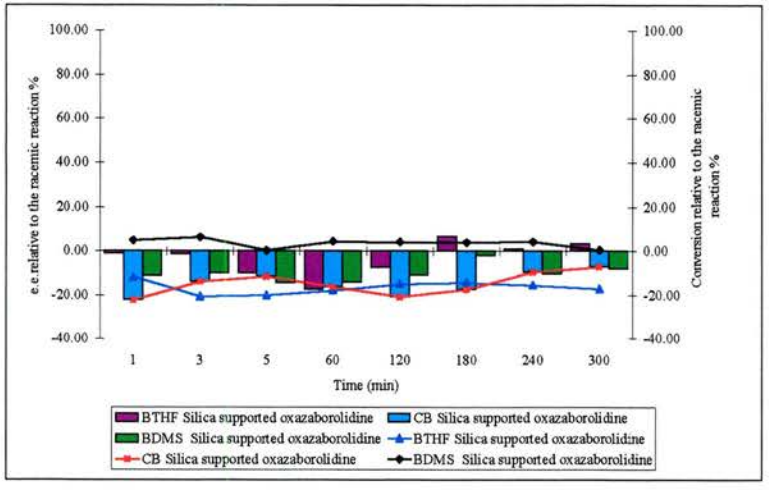




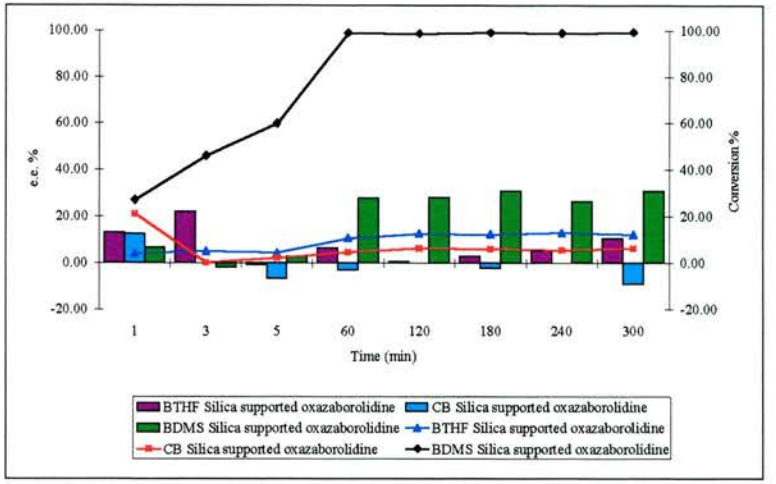
Effect of 0.1 equivalent of silica supported oxazaborolidine.

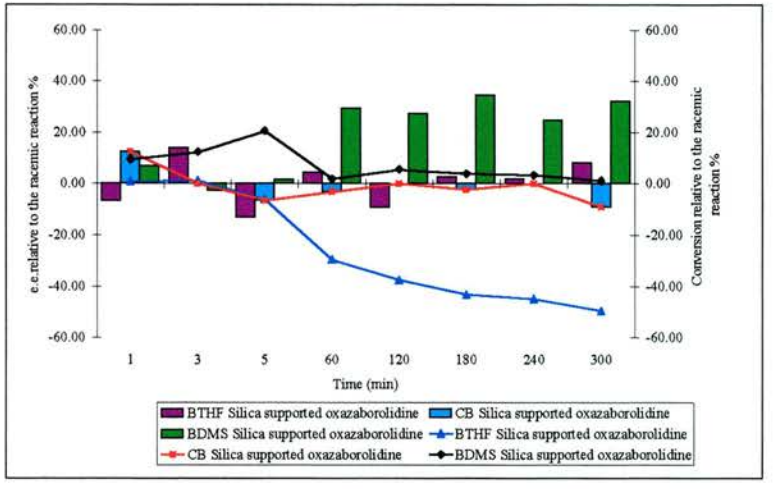
Imine:





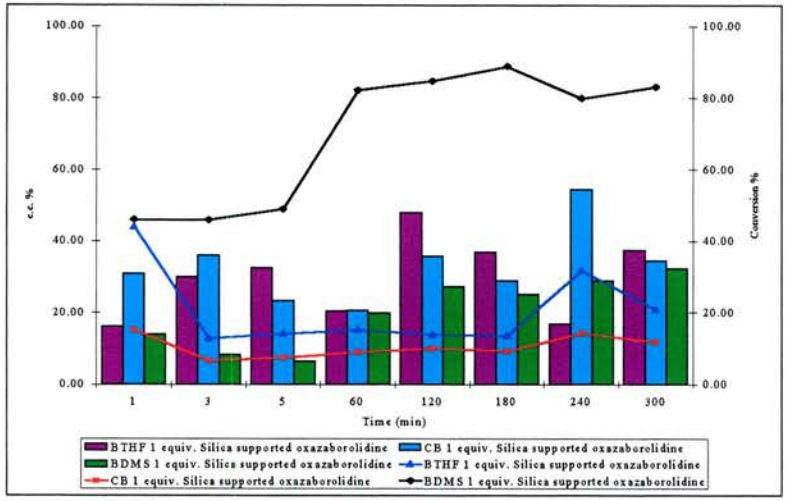
Ketone:

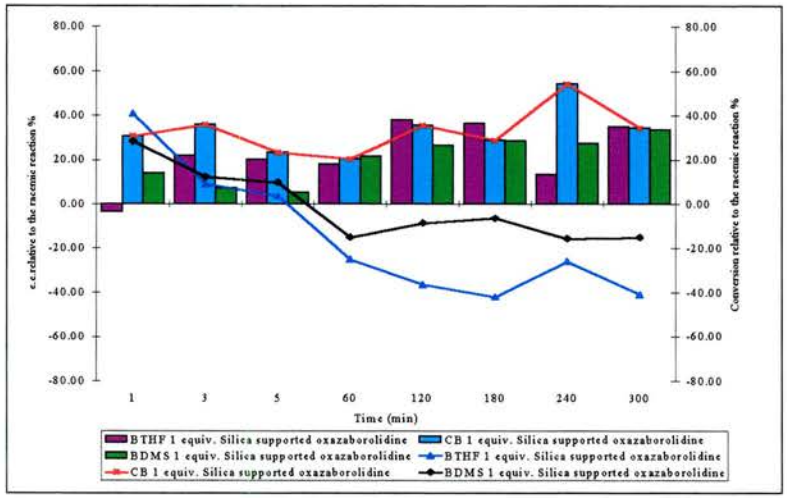




Effect of 1 equivalent silica supported oxazaborolidine.

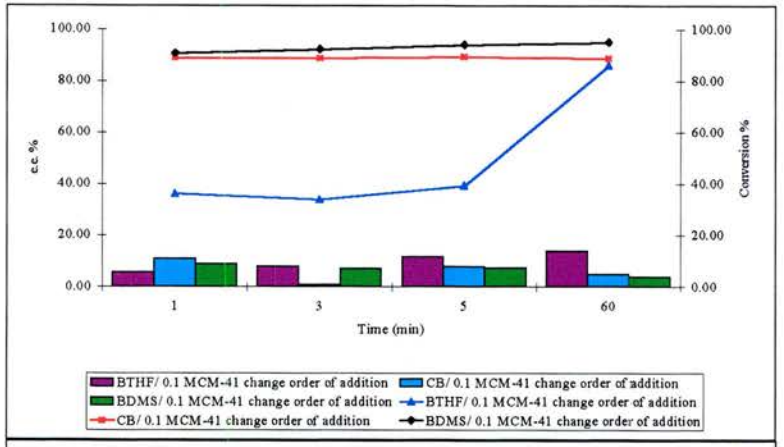
Ketone:

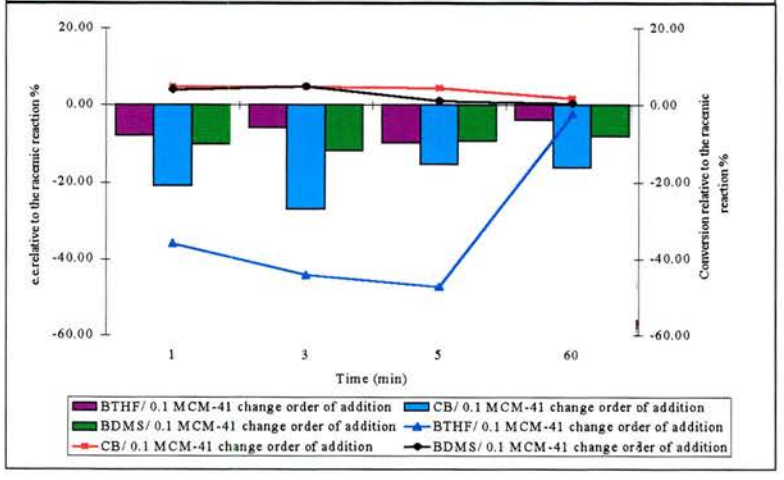




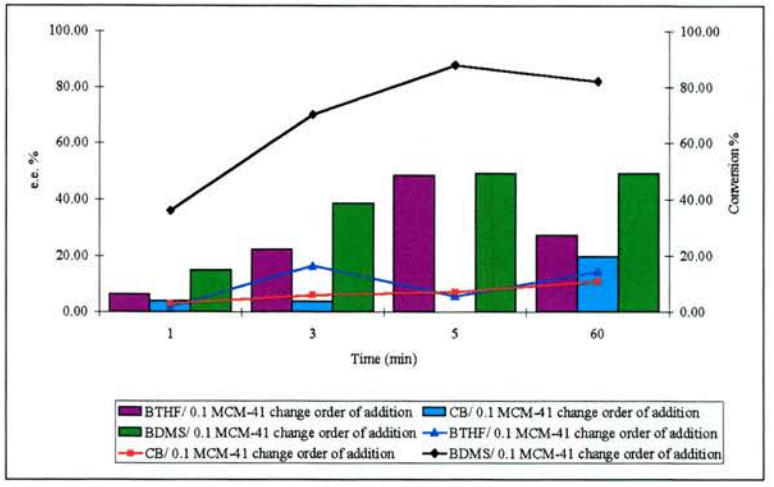
Effect of changing order of addition for 0.1 equiv. of MCM-41 supported oxazaborolidine. (Borane + oxazaborolidine then add substrate)

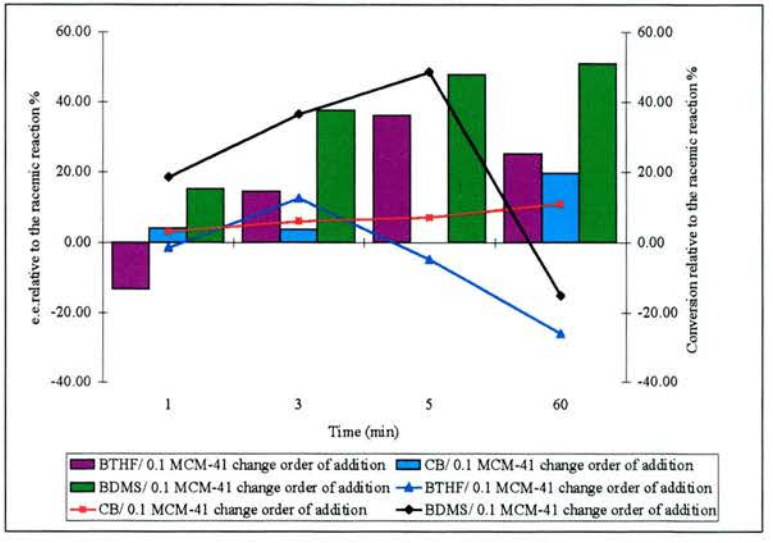
Imine:





Ketone:





6.8 References

1 P. W. Atkins, *Physical Chemistry*, Oxford University Press, 1990, p. 618.

2 J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt, C. T-W. Chu, D. H, Olson, E. W. Sheppard, S. B. McCullen, J. B. Higgins, J. L. Schlenker, *J. Am. Chem. Soc.*, 1992, **114**, 10834.

3 E. Kaiser, R. L. Colescott, C. D. Bossinger, *Anal. Biochem.*, 1970, **34**, 595.